DRAFT
TOXICOLOGICAL PROFILE FOR
HYDROGEN SULFIDE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

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UPDATE STATEMENT

A Toxicological Profile for Hydrogen Sulfide was released in 1999. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE
Mailstop F-32
Atlanta, Georgia 30333

FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Comments should be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, N.E.
Mail Stop F-32
Atlanta, Georgia 30333

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 7, 2003 (68 FR 63098). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999 (64 FR 56792) and October 25, 2001 (66 FR 54014) . Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Julie Louise Gerberding, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6	**How Can (Chemical X) Affect Children?**
Section 1.7	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.8	**Biomarkers of Exposure and Effect**
Section 3.11	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone:	1-888-42-ATSDR or (404) 498-0110	***Fax:***	(770) 488-4178
E-mail:	atsdric@cdc.gov	***Internet***:	http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental*

Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHOR(S):

Selene Chou, Ph.D.
ATSDR, Division of Toxicology, Atlanta, GA

Mike Fay, Ph.D.
ATSDR, Division of Toxicology, Atlanta, GA

Sam Keith, M.S.
ATSDR, Division of Toxicology, Atlanta, GA

Lisa Ingerman, Ph.D.
Syracuse Research Corporation, North Syracuse, NY

Lara Chappell, Ph.D.
Syracuse Research Corporation, North Syracuse, NY

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for hydrogen sulfide. The panel consisted of the following members:

1. Steven C. Lewis, Ph.D., DABT, President and Principal Scientist, Integrative Policy & Science, Inc.; Adjunct Professor, Robert Wood Johnson Medical School, Washington, New Jersey;

2. John A. Pickrell, Ph.D., Associate Professor Environmental Toxicology, College of Veterinary Medicine, Kansas State University, Manhattan, Kansas;

3. Roger P. Smith, Ph.D., Irene Heinz Given Professor of Pharmacology and Toxicology, Emeritus, Dartmouth Medical School, Hanover, New Hampshire;

4. Alan Hall, M.D., FACEP, Clinical Assistant Professor, University of Colorado School of Medicine, Denver, Colorado;

5. Edwin Kinkead, B.S., Private Consultant, Bonita Springs, Florida; and

6. James Way, Ph.D., Professor, Texas A & M University, College Station, Texas.

These experts collectively have knowledge of hydrogen sulfide's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about hydrogen sulfide and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. EPA then places these sites on the National Priorities List (NPL) and targets them for federal long-term cleanup activities. Hydrogen sulfide has been found in at least 35 of the 1,647 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the number of sites at which hydrogen sulfide is found could increase as more sites are evaluated. This information is important because these sites may be sources of exposure, and exposure to this substance can harm you.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you contact it—by breathing, eating, or drinking the substance or by skin contact.

Many factors will determine whether exposure to hydrogen sulfide will harm you. These factors include the dose (how much), the duration (how long), and the way you contact it. You also must consider any other chemicals to which you are exposed and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS HYDROGEN SULFIDE?

Hydrogen sulfide (H_2S) is a poisonous, flammable, colorless gas with a characteristic odor of rotten eggs. Other names for hydrogen sulfide include hydrosulfuric acid, sewer gas, hydrogen sulphide, and stink damp. People usually can smell hydrogen sulfide at low concentrations in air, ranging from 0.0005 to 0.3 parts per million (ppm) (0.0005–0.3 parts of hydrogen sulfide in 1 million parts of air); however, at high concentrations, a person might lose their ability to smell it. This can make hydrogen sulfide very dangerous.

Hydrogen sulfide occurs both naturally and from human-made processes. It is in the gases from volcanoes, sulfur springs, undersea vents, swamps, and stagnant bodies of water and in crude petroleum and natural gas. Hydrogen sulfide also is associated with municipal sewers and sewage treatment plants, swine containment and manure-handling operations, and pulp and paper operations. Industrial sources of hydrogen sulfide include petroleum refineries, natural gas plants, petrochemical plants, coke oven plants, food processing plants, and tanneries. Bacteria found in your mouth and gastrointestinal tract produce hydrogen sulfide from bacteria decomposing in materials that contain vegetable or animal proteins. Hydrogen sulfide is one of the principal components in the natural sulfur cycle. You will find more about the properties, production, and use of hydrogen sulfide in Chapters 4 and 5.

1.2 WHAT HAPPENS TO HYDROGEN SULFIDE WHEN IT ENTERS THE ENVIRONMENT?

Hydrogen sulfide is released primarily as a gas and spreads in the air. However, in some instances, it may be released in the liquid waste of an industrial facility or as the result of a natural event. When hydrogen sulfide is released as a gas, it remains in the atmosphere for an average of 18 hours. During this time, hydrogen sulfide can change into sulfur dioxide and sulfuric acid. Hydrogen sulfide is soluble in water, and is a weak acid in water. You will find more about what happens to hydrogen sulfide when it enters the environment in Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO HYDROGEN SULFIDE?

Your body makes small amounts of hydrogen sulfide. Hydrogen sulfide is produced by the natural bacteria in your mouth and is a component of bad breath (halitosis). Breakdown of sulfur-containing proteins by bacteria in the human intestinal tract also produces hydrogen sulfide. The levels of hydrogen sulfide in air and water are typically low. The amount of hydrogen sulfide in the air in the United States is 0.11–0.33 parts per billion (ppb) (one thousandth of a ppm). In undeveloped areas of the United States, concentrations have been reported at 0.02–0.07 ppb. The amount of hydrogen sulfide in surface water is low because

hydrogen sulfide readily evaporates from water. Groundwater concentrations of hydrogen sulfide generally are less than 1 ppm; however, measured sulfur concentrations in surface and waste waters have ranged from slightly less than 1 to 5 ppm. Household exposures to hydrogen sulfide can occur through misuse of drain cleaning materials. Hydrogen sulfide can be found in well water and formed in hot water heaters, giving tap water a rotten egg odor. Cigarette smoke and emissions from gasoline vehicles contain hydrogen sulfide. The general population can be exposed to lower levels from accidental or deliberate release of emissions from pulp and paper mills; from natural gas drilling and refining operations; and from areas high geothermal activity, such as hot springs.

People who work in certain industries can be exposed to higher levels of hydrogen sulfide than the general population. These industries include rayon textiles manufacturing, pulp and paper mills, petroleum and natural gas drilling operations, and waste water treatment plants. Workers on farms with manure storage pits or landfills can be exposed to higher levels of hydrogen sulfide than the general population. As a member of the general public, you might be exposed to higher-than-normal levels of hydrogen sulfide if you live near a waste water treatment plant, a gas and oil drilling operation, a farm with manure storage or livestock confinement facilities, or a landfill. Exposure from these sources is mainly from breathing air that contains hydrogen sulfide. You will find further information about hydrogen sulfide exposure in Chapter 6.

1.4 HOW CAN HYDROGEN SULFIDE ENTER AND LEAVE MY BODY?

Hydrogen sulfide enters your body primarily through the air you breathe. It also can enter your body through the skin. Hydrogen sulfide is a gas, so you would not likely be exposed to it by ingestion. When you breathe air containing hydrogen sulfide or when hydrogen sulfide comes into contact with skin, it is absorbed into the blood stream and distributed throughout the body. In the body, hydrogen sulfide is primarily converted to sulfate and is excreted in the urine. Additional information about how hydrogen sulfide can enter or leave your body is discussed in Chapter 3.

1.5 HOW CAN HYDROGEN SULFIDE AFFECT MY HEALTH?

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways to treat people who have been harmed.

One way to learn whether a chemical will harm people is to determine how the body absorbs, uses, and releases the chemical. For some chemicals, animal testing may be necessary. Animal testing can help identify health problems, such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method for getting information needed to make wise decisions that protect public health. Scientists have the responsibility to treat research animals with care and compassion. Scientists must comply with strict animal-care guidelines because laws today protect the welfare of research animals.

Exposure to low concentrations of hydrogen sulfide may cause irritation to the eyes, nose, or throat. It may also cause difficulty in breathing for some asthmatics. Brief exposures to high concentrations of hydrogen sulfide (greater than 500 ppm) can cause a loss of consciousness. In most cases, the person appears to regain consciousness without any other effects. However, in many individuals, there may be permanent or long-term effects such as headaches, poor attention span, poor memory, and poor motor function. No health effects have been found in humans exposed to typical environmental concentrations of hydrogen sulfide (0.00011–0.00033 ppm). Deaths due to breathing in large amounts of hydrogen sulfide have been reported in a variety of different work settings, including sewers, animal processing plants, waste dumps, sludge plants, oil and gas well drilling sites, and tanks and cesspools.

Very little information is available about health problems that could occur from drinking or eating something with hydrogen sulfide in it. Scientists have no reports of people poisoned by such exposures. Pigs that ate feed containing hydrogen sulfide experienced diarrhea for a few days and lost weight after about 105 days.

Scientists have little information about what happens when you are exposed to hydrogen sulfide by getting it on your skin, although they know that care must be taken with the compressed

liquefied product to avoid frostbite. Hydrogen sulfide will irritate your eyes if you are exposed to the gas. These types of exposures are more common in certain kinds of jobs.

Hydrogen sulfide has not been shown to cause cancer in humans, and its possible ability to cause cancer in animals has not been studied thoroughly. Hydrogen sulfide has not been classified for its ability to cause or not cause cancer. Scientist have some evidence that exposure to hydrogen sulfide can increase miscarriages in people, but the studies where this was reported were complicated by exposures to other chemicals and lack of information about the amount of exposure to hydrogen sulfide.

1.6 HOW CAN HYDROGEN SULFIDE AFFECT CHILDREN?

This section discusses potential health problems in people from exposures during conception to maturity (18 years of age).

Children are likely to be exposed to hydrogen sulfide in the same manner as adults, except for adults at work. However, because hydrogen sulfide is heavier than air and because children are shorter than adults, children sometimes are exposed to more hydrogen sulfide than adults. Health problems in children who have been exposed to hydrogen sulfide have not been studied much. Exposed children probably will experience effects similar to those experienced by exposed adults. Whether children are more sensitive to hydrogen sulfide exposure than adults or whether hydrogen sulfide causes birth defects in people is not known. For more information about the potential health effects of hydrogen sulfide on children, see Sections 3.7 and 6.6.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO HYDROGEN SULFIDE?

If your doctor finds you (or a family member) have been exposed to substantial amounts of hydrogen sulfide, ask whether your children also might have been exposed. Your doctor might need to ask your state health department to investigate.

Families can be exposed to more hydrogen sulfide than the general population if they live near natural or industrial sources of hydrogen sulfide, such as hot springs, manure holding tanks, or pulp and paper mills. However, their exposure levels are unlikely to approach those that sicken people exposed at work.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO HYDROGEN SULFIDE?

Hydrogen sulfide can be measured in exhaled air, but samples must be taken within 2 hours after exposure to be useful. A more reliable test to determine if you have been exposed to hydrogen sulfide is the measurement of thiosulfate levels in urine. This test must be done within 12 hours of exposure. Both tests require special equipment, which is not routinely available in a doctor's office. Samples can be sent to a special laboratory for the tests. These tests can tell whether you have been exposed to hydrogen sulfide, but they cannot determine exactly how much hydrogen sulfide you have been exposed to or whether harmful effects will occur.

See Chapters 3 and 7 for more information on tests for exposure to hydrogen sulfide.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations *can* be enforced by law. EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health but *cannot* be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention (CDC) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as “not-to-exceed” levels—in other words, levels of a toxic substance in air, water, soil, or food that do not exceed critical levels that usually are based on levels that affect animals; they are then adjusted to levels that will help protect people. Sometimes these not-to-exceed levels differ among federal agencies because the agencies used different exposure times (for example, an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are updated periodically as more information becomes available. For the most current information, check with the federal agency that provides it.

OSHA has established an acceptable ceiling concentration of 20 ppm for hydrogen sulfide in the workplace, with a maximum level of 50 ppm allowed for 10 minutes maximum duration if no other measurable exposure occurs. NIOSH has set a maximum Recommended Exposure Limit (REL) ceiling value of 10 ppm for 10 minutes maximum duration. A more complete listing of federal and state regulations and recommendations is found in Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and

technical assistance number at 1-888-42ATSDR (1-888-422-8737), by e-mailing atsdric@cdc.gov, or by writing to

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

For-profit organizations may request copies of final Toxicological Profiles from

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO HYDROGEN SULFIDE IN THE UNITED STATES

Hydrogen sulfide (H_2S) is a poisonous, colorless gas with a characteristic odor of rotten eggs. It naturally occurs in the gases from volcanoes, sulfur springs, undersea vents, swamps and stagnant bodies of water and in crude petroleum and natural gas. Additionally, bacteria, fungi, and actinomycetes release hydrogen sulfide during the decomposition of sulfur-containing proteins and by the direct reduction of sulfate (SO_4^{2-}). Hydrogen sulfide is frequently encountered in various industries and may be released to the environment as a result of their operations. Some of these industries include natural gas production, municipal sewage pumping and treatment plants, landfilling, swine containment and manure handling, pulp and paper production, construction in wetlands, asphalt roofing, pelt processing, petroleum refining, petrochemical synthesis, coke production plants, viscose rayon manufacture, sulfur production, iron smelting, and food processing.

Ambient air concentrations of hydrogen sulfide from natural sources range between 0.11 and 0.33 ppb. Concentrations of hydrogen sulfide in urban areas are generally <1 ppb. Much higher levels (often exceeding 90 ppb) have been detected in communities living near natural sources of hydrogen sulfide or near industries releasing hydrogen sulfide.

Humans may be exposed to hydrogen sulfide both from its endogenous production or from exogenous sources. Most endogenous production apparently results from the metabolism of sulfhydryl-containing amino acids (e.g., cysteine) by bacteria present in both the intestinal tract and the mouth; however, it is also produced in the brain and several smooth muscles (e.g., thoracic aorta) by enzymes found in these tissues. Hydrogen sulfide produced in the mouth is a component of bad breath (halitosis); concentrations between 1 and 100 ppb have been measured in mouth air. It is generated in the large intestine by the bacterial reduction of inorganic sulfate and sulfite, and by fermentation of sulfur-containing amino acids. It can compose up to 10% of intestinal gases. In flatus, hydrogen sulfide concentrations as high as 18 ppm were recorded by Kirk in individuals on a normal diet. In these experiments, between 40 and 90% of normal individuals produced hydrogen sulfide; mean values over a 4-year period were between 1 and 4 ppm. Sulfide concentrations in whole blood samples from six healthy adults were found to range from 10 to 100 µmol/L.

There is considerable individual variability in the odor threshold for hydrogen sulfide in humans; the thresholds can range from 0.0005 to 0.3 ppm. However, at concentrations of 100 ppm and higher, individuals may not detect hydrogen sulfide odor due to damage.

2.2 SUMMARY OF HEALTH EFFECTS

The general population is primarily exposed to hydrogen sulfide via the inhalation route. Although oral and dermal absorption can also occur, these routes only contribute small amounts to the overall body burden. Information on the toxicity of hydrogen sulfide in humans comes from case reports, occupational studies, and community studies. Hydrogen sulfide tends to be a problem in communities located near certain types of industrial sites, including pulp and paper mills, gas refineries, or geothermal power plants; interpretation of the community studies is limited by exposure to other chemicals. The human data suggest that the respiratory tract and nervous system are the most sensitive targets of hydrogen sulfide toxicity. The most commonly reported nonlethal effect found in individuals acutely exposed to high concentrations of hydrogen sulfide is unconsciousness followed by apparent recovery, colloquially referred to as knockdown. In most cases, actual exposure concentrations and durations are not known; estimates suggest that the concentrations exceed 500 ppm and the durations are short, typically less than 1 hour. Although there is an apparent recovery, many individuals report permanent or persistent neurological effects including headaches, poor concentration ability and attention span, impaired short-term memory, and impaired motor function. Respiratory distress or arrest and pulmonary edema are also associated with exposure to very high concentrations of hydrogen sulfide; it is believed that these respiratory effects are secondary to central nervous system depression or due to tissue hypoxia. Cardiovascular effects (e.g., cardiac arrhythmia and tachycardia) have also been observed following an acute exposure to high concentrations of hydrogen sulfide.

Exposure to lower concentrations of hydrogen sulfide can result in less severe neurological and respiratory effects. Reported neurological effects include incoordination, poor memory, hallucinations, personality changes, and anosmia (loss of sense of smell); the respiratory effects include nasal symptoms, sore throat, cough, and dyspnea. Impaired lung function has also been observed in asthmatics acutely exposed to 2 ppm hydrogen sulfide; no alterations in lung function were observed in studies of non-asthmatic workers.

Animal studies confirm these human data, which suggest that the respiratory tract and the nervous system are the most sensitive targets of hydrogen sulfide toxicity. As with humans, unconsciousness was observed in rats exposed to very high concentrations of hydrogen sulfide (800 ppm); central nervous system depression, as evidenced by lethargy and pulmonary edema, was observed in rats exposed to 400 ppm hydrogen sulfide for 4 hours. Decreased performance in neurological tests has been observed in rats exposed to 80–200 ppm hydrogen sulfide for 5 days to 11 weeks. Damage to the nasal olfactory epithelium is also observed in rats exposed to lower levels of hydrogen sulfide for an acute or intermediate duration; the adverse effect levels are 80 ppm (3 hours/day for 5 days) and 30 ppm (6 hours/day, 7 days/week for 10 weeks) following acute- or intermediate-duration exposure, respectively.

Information on the toxicity of hydrogen sulfide following oral or dermal/ocular exposure is limited. Oral exposure data are limited to a single pig study examining the effects of hydrogen sulfide in feed. Observed effects included a diarrheic digestive disorder and decreased body weight gain. Exposure to hydrogen sulfide gas can result in a number of ocular effects, including keratoconjunctivitis, punctuate corneal erosion, blepharospasm, lacrimation, and photophobia in humans. A community exposure study found a concentration-related increase in the prevalence of eye symptoms in residents exposed to low (daily mean of total reduced sulfur <10 $\mu g/m^3$), medium (10–30 $\mu g/m^3$), or high (>30 $\mu g/m^3$) levels. Although hydrogen sulfide was the primary constituent of the total reduced sulfur levels, other sulfur compounds, as well as other air pollutants, may have contributed to the eye irritation.

There are limited human data suggesting that maternal or paternal exposure to hydrogen sulfide can increase the risk of spontaneous abortion among rayon textile, paper produces, or petrochemical workers (or their spouses). However, the subjects (or their spouses) were exposed to a number of other hazardous chemicals, which may have contributed to the increased risk. No significant alterations in reproductive performance were observed in rats exposed to 10–80 ppm hydrogen sulfide for an intermediate duration. The available animal data suggest that hydrogen sulfide is not a developmental toxicant at concentrations of 80 ppm and lower. No structural anomalies, developmental delays, performance in developmental neurobehavioral tests, or brain histology were observed in a well-conducted rat study. Another study found alterations in Purkinje cell growth in the offspring of rats exposed to 20 or 50 ppm hydrogen sulfide during the gestation and lactation periods. The toxicological significance of this finding in the absence of alterations in neurobehavioral performance is not known.

There are limited data on the potential of hydrogen sulfide to induce cancer in humans. One study found significant increases in the risk of developing cancers of the trachea, bronchus, and lung among residents

exposed to high levels of naturally occurring hydrogen sulfide. However, the authors noted that the elevated disease rates were consistent with exposure to high concentrations of hydrogen sulfide and mercury; the contribution of mercury to the overall respiratory tract cancer rates cannot be determined from these data. Another study did not find significant alterations in cancer incidences among residents living near natural gas refineries. The carcinogenicity of hydrogen sulfide has not been assessed in animal studies.

A greater detailed discussion of the hydrogen sulfide-induced respiratory effects and neurological effects follows. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for additional information of these effects and other health effects.

Respiratory Effects. Exposure to very high concentrations of hydrogen sulfide can result in respiratory arrest and/or pulmonary edema. Numerous case reports suggest that these effects can occur after a brief exposure to hydrogen sulfide. Although the exact mechanism is not known, there is strong evidence to suggest that the rapid respiratory failure and possibly the pulmonary edema are secondary to the action of hydrogen sulfide on the respiratory center of the brain. There is also some evidence that the respiratory failure and pulmonary edema may be due to a dose-dependent inhibition of cytochrome oxidase in lung mitochondria, the terminal step in oxidative metabolism, resulting in tissue hypoxia. At low concentrations, hydrogen sulfide is a respiratory irritant. Residents living near industries emitting hydrogen sulfide, such as paper mills, animal slaughter facilities, or tanneries, reported nasal symptoms, cough, or increased visits to the hospital emergency room due to respiratory symptoms (including asthma). In general, exposure to hydrogen sulfide has not resulted in significant alterations in lung function. No alterations in lung function were observed in workers chronically exposed to 1–11 ppm hydrogen sulfide. However, there is some evidence to suggest that asthmatics may be a sensitive subpopulation. No statistical alterations in lung function were observed in a group of 10 asthmatics exposed to 2 ppm hydrogen sulfide for 30 minutes. However, increased airway resistance and decreased specific airway conductance, implying bronchial obstruction, were observed in 2 out of the 10 subjects.

Although the human data are useful in establishing the respiratory tract as a target of toxicity, concentration-response relationships cannot be established for most of these studies because exposure levels were not monitored or the subjects were exposed to several sulfur compounds. Animal data provide strong evidence that the respiratory tract is a sensitive target of hydrogen sulfide toxicity and can be used to establish concentration-response relationships. Damage to the nasal olfactory epithelium has been observed in rats exposed to hydrogen sulfide for acute or intermediate durations. Loss of olfactory

neurons and basal cell hyperplasia were observed in rats exposed to 30 ppm and higher for 6 hours/day, 7 days/week for 10 or 13 weeks. The severity of the olfactory neuron loss was concentration-related; however, an inverse relationship between severity and concentration was observed for the basal cell hyperplasia suggesting that as the concentration increased, the ability of the olfactory epithelium to regenerate decreased. Similar effects were observed in rats exposed to hydrogen sulfide once or repeatedly for 5 days; however, higher concentrations were needed to elicit a significant response. Intermediate-duration exposure (6 hours/day, 5 days/week for 13 weeks) resulted in inflammation of the squamous portion of the nasal mucosa in mice exposed to 80 ppm and loss of olfactory neurons in mice exposed to 30 ppm and higher.

Neurological Effects. A brief exposure to very high concentrations of hydrogen sulfide can result in unconsciousness in humans and animals followed by an apparent full recovery upon exposure termination (some human case reports note that the subjects recovered after administration of oxygen). Human data are not reliable for establishing the threshold for this effect. In rats, the threshold for severe central nervous system depression is between 400 and 800 ppm; exposure to 400 ppm was associated with lethargy. As noted previously, persistent neurological effects have been reported in humans recovering from hydrogen-sulfide induced unconsciousness. These effects include headaches, poor concentration ability and attention span, impaired short-term memory, and impaired motor function.

Exposure to hydrogen sulfide can also result in neurobehavioral effects in humans and animals. Alterations in balance, reaction time, visual field, and verbal recall were observed in individuals exposed to high concentrations of hydrogen sulfide for an acute duration and in individuals exposed to lower levels of hydrogen sulfide for a chronic duration; no monitoring data were provided. The severity of effects appeared to be related to the duration of exposure as well as the exposure concentration. Several animal studies provide suggestive evidence that hydrogen sulfide exposure results in a decrease in motor activity and task response rate; the lowest adverse effect level for altered neurobehavioral performance is the decreased spontaneous motor activity observed in rats receiving nose-only exposure to 80 ppm, 3 hours/day for 5 days. A rat study found that intermediate-duration exposure to hydrogen sulfide did not adversely affect memory; however, learning a new complex task was adversely affected at 125 ppm (4 hours/day, 5 days/week).

2.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRL

- An MRL of 0.2 ppm has been derived for acute-duration inhalation exposure to hydrogen sulfide.

A small number of controlled exposure studies have examined the acute toxicity of hydrogen sulfide in humans; most of these have focused on potential respiratory and metabolic effects. No significant alterations in lung function (forced lung vital capacity, forced expiratory volume, bronchial responsiveness to a histamine challenge, airway resistance, and specific airway conductance) were observed in asthmatics exposed to 2 ppm for 30 minutes (Jappinen et al. 1990). However, 2 of the 10 subjects had >30% changes in airway resistance and specific airway conductance, implying bronchial obstruction. Three of the subjects also reported headaches. A series of studies conducted by Bhambhani and associates examined the potential of hydrogen sulfide to induce respiratory and metabolic effects in exercising adults. No significant alterations in lung function were observed in individuals exposed to 10 ppm for 15 minutes (Bhambhani et al. 1996a), but increases in blood lactate levels were observed in subjects exposed to 5 or 10 ppm (Bhambhani and Singh 1991; Bhambhani et al. 1997). The study authors noted that the increase in lactate levels suggested an increased dependence on anaerobic metabolism, which may have resulted from reduced oxygen availability due to detoxification of hydrogen sulfide by oxyhemoglobin or inhibition of cytochrome oxidase in exercising tissue (Bhambhani 1999).

Animal studies have reported a variety of respiratory effects following acute-duration exposure to hydrogen sulfide. Damage to the nasal olfactory epithelium was observed in rats exposed to 400 ppm for 4 hours (Lopez et al. 1988b), 200 ppm for 3 hours (Brenneman et al. 2002), or 80 ppm 3 hours/day for 5 days (Brenneman et al. 2002). Pulmonary edema has been observed in rats exposed to 83 or 375 ppm for 4 hours (Lopez et al. 1988a; Prior et al. 1990). Neurological effects include decreased spontaneous motor activity in rats exposed to 80 ppm, 3 hours/day for 5 days (Struve et al. 2001), impaired performance on a discriminated avoidance task in rats exposed to 200 ppm for 2 hours (Higuchi and Fukamachi 1977), lethargy in rats exposed to 400 ppm for 4 hours (Lopez et al. 1988b), and unconsciousness in rats exposed to 800 ppm for 20 minutes (Beck et al. 1979).

The Jappinen et al. (1990) study, which found suggestive evidence of bronchial obstruction among asthmatics exposed to 2 ppm hydrogen sulfide for 30 minutes, was selected as the basis of the MRL. This minimally adverse effect level is supported by the lowest-observed-adverse-effect level (LOAEL) of

5 ppm for increased blood lactate levels observed in exercising subjects (Bhambhani et al. 1996b). The Jappinen et al. (1990) study was selected over the Bhambhani et al. (1996b) study because the Bhambhani studies involved mouth-only exposure so that the subjects could not smell the hydrogen sulfide. The MRL was calculated by dividing the unadjusted LOAEL by an uncertainty factor of 9 (3 for use of a minimal LOAEL and 3 for human variability). Further details on the derivation of this MRL can be found in the MRL worksheets in Appendix A of this profile.

- An MRL of 0.02 ppm has been derived for intermediate-duration inhalation exposure to hydrogen sulfide.

There are limited data on the toxicity of hydrogen sulfide in humans following intermediate-duration exposure. Acute- and chronic-duration studies suggest that the respiratory tract and nervous system are sensitive targets of hydrogen sulfide.

Intermediate-duration animal studies support the identification of the respiratory tract and nervous system as sensitive targets. Exposure of rats and mice to low hydrogen sulfide concentrations have resulted in histological damage to the upper respiratory tract. Brenneman et al. (2000) reported significant concentration-related increases in the incidence and severity of lesions to the nasal olfactory epithelium in rats exposed to hydrogen sulfide for 10 weeks. The effects consisted of olfactory neuron loss and basal cell hyperplasia in rats exposed to 30 or 80 ppm, 6 hours/day, 7 days/week for 10 weeks; no adverse effects were observed at 10 ppm. In contrast, earlier studies conducted by CIIT (1983b, 1983c) did not find significant alterations in the nasal turbinates of Sprague-Dawley or Fischer-344 (F-344) rats exposed to 80 ppm or less hydrogen sulfide, 6 hours/day, 5 days/week for 13 weeks. Inflammation of the squamous portion of the nasal mucosa was observed in mice exposed to 80 ppm hydrogen sulfide, 6 hours/day, 5 days/week for 13 weeks (CIIT 1983a); the no-observed-adverse-effect level (NOAEL) for this effect is 30 ppm. However, a re-examination of the histological specimens from this study (Dorman et al. 2004) revealed a statistically significant increase in the incidence of olfactory neuron loss in Sprague-Dawley rats, F-344 rats, and B6C3F$_1$ mice exposed to 30 or 80 ppm; no lesions were observed at 10 ppm. In addition, increases in the incidence of bronchiolar epithelial hyperplasia and hypertrophy were observed in female Sprague-Dawley rats exposed to 30 or 80 ppm and male Sprague-Dawley and F-344 rats exposed to 80 ppm. The sensitivity of the olfactory epithelium has also been confirmed by acute-duration studies; degeneration of the olfactory epithelium was observed in rats exposed to 400 ppm hydrogen sulfide for 4 hours (Lopez et al. 1988b), rats exposed to 200 ppm for 3 hours (Brenneman et al. 2002), and rats exposed to 80 ppm, 3 hours/day for 5 days (Brenneman et al. 2002). Additionally, data collected using a computational fluid dynamics model of the rat nasal epithelium (Moulin et al. 2002)

suggest that the olfactory epithelium is more sensitive than the nasal respiratory epithelium despite the higher hydrogen sulfide flux (a surrogate for dose) to the regions lined with respiratory epithelium compared to regions lined with olfactory epithelium. Within the areas of the nose lined with olfactory epithelium, a high correlation between predicted hydrogen sulfide flux and the incidence of olfactory lesion was found.

The neurotoxicity of hydrogen sulfide in mature animals following intermediate-duration exposure has been assessed in studies examining brain weight, neurological function (posture, gait, tone of facial muscles, and pupillary reflexes), and histopathology; neurobehavioral performance has not been adequately assessed in longer duration studies. A 5% decrease in absolute brain weight was observed in Sprague-Dawley rats exposed to 80 ppm hydrogen sulfide 6 hours/day, 5 days/week for 13 weeks; no alterations were observed at 30 ppm (CIIT 1983c). No alterations in histopathology or neurological function were observed in these rats (CIIT 1983c) or in similarly exposed F-344 rats (CIIT 1983b) or B6C3F_1 mice (CIIT 1983a). Neurodevelopmental toxicity studies have found some alterations that are suggestive of neurotoxicity. The suggestive findings in the offspring of rats exposed for 7 hours/day on gestational day 5 through postnatal day 21 include alterations in the architecture and growth characteristics of Purkinje cell dendritic fields at 20 ppm (Hannah and Roth 1991), decreases in norepinephrine and increases in serotonin in the frontal cortex at 20 ppm (Skrajny et al. 1992), and decreases in brain amino acid levels were observed at 75 ppm (Hannah et al. 1989, 1990). However, no alterations in neurobehavioral performance (assessed via motor activity, passive avoidance, acoustic startle, functional observation battery), delays in development (pinnae detachment, surface righting, incisor eruption, negative geotaxis, and eyelid detachment), or neuropathology were observed in the offspring of rats exposed for 2 weeks prior to mating, during mating, on gestational days 5–19, and on postnatal days 5–18 (Dorman et al. 2000). These data suggest that exposures of 20–80 ppm may result in subclinical alterations in neurochemistry and neuroanatomy.

The Brenneman et al. (2000) study was selected as the basis of the intermediate-duration inhalation MRL. In this study, groups of 12 male Sprague-Dawley rats were exposed to 0, 10, 30, or 80 ppm hydrogen sulfide for 6 hours/day, 7 days/week for 10 weeks. Parameters used to assess toxicity were limited to extensive histopathological examination of the nasal cavity (six transverse sections examined via light microscopy). Nasal lesions were limited to the olfactory mucosa in rats exposed to 30 or 80 ppm and consisted of multifocal, bilaterally symmetrical olfactory neuron loss and basal cell hyperplasia affecting the lining of the dorsal medial meatus and the dorsal and medial regions of the ethmoid recess. The severity of the olfactory lesions was scored as 1 mild, 2 moderate, or 3 severe. For the olfactory neuron

loss, the mild, moderate, or severe severity scores corresponded to 26–50, 51–75, and 76–100%, respectively, reduction in the normal thickness of the olfactory neuron layer; for the basal cell hyperplasia, mild, moderate, or severe severity scores corresponded to 1–33, 34–67, or 68–100% of the normal thickness of the olfactory neuron cell layer replaced by basal cells. No olfactory lesions were observed in the controls or rats exposed to 10 ppm. At 30 ppm, olfactory neuron loss was observed at nasal levels 4 (11/12, severity 1.4) and 5 (9/12, severity 1.1) and basal cell hyperplasia was observed at nasal levels 4 (10/12, severity 1.8) and 5 (11/12, severity 1.3). At 80 ppm, olfactory neuron loss was observed at levels 3 (8/8, severity 2.4), 4 (12/12, severity 2.4), 5 (11/12, severity 1.5), and 6 (5/12, severity 1.2-incidence not statistically significant) and basal cell hyperplasia was observed at nasal levels 4 (12/12, severity 1.2), 5 (11/12, severity 1.3), and 6 (6/12, severity 1.0).

The Brenneman et al. (2000) study was selected over the neurodevelopmental studies (Hannah and Roth 1991; Skrajny et al. 1992), which identified a slightly lower LOAEL (20 ppm) because the effect has been confirmed by other studies (Brenneman et al. 2002; Lopez et al. 1988b) and the adversity of these subclinical alterations in neurochemistry and neuroanatomy in the absence of neurological performance alterations is not known. As discussed by Ferguson (1996), prenatal exposure to ionizing radiation can result in misalignment of Purkinje cells in the cerebellum; clinical signs associated with these neuroanatomical alterations include hypoactivity, ataxia, tremors, and learning deficits. Although a direct comparison of the Purkinje cell alterations reported in the Hannah and Roth (1991) study and those resulting from ionizing radiation exposure cannot be made because the Hannah and Roth study involved examination of a single Purkinje cell rather than cerebellar sections, it may be reasonable to predict that the clinical manifestations of the Purkinje cell damage would be similar. The similarity of the LOAELs for nasal effects and neurodevelopmental effects suggest that an MRL derived for one would be protective of the other.

The MRL of 0.02 ppm was calculated by dividing the human equivalent concentration of the NOAEL ($NOAEL_{HEC}$) by an uncertainty factor of 30 (3 for extrapolation from animals using dosimetric adjustments and 10 for human variability). Further details on the derivation of this MRL can be found in the MRL worksheets in Appendix A of this profile.

A chronic-duration inhalation MRL was not derived since data were insufficient.

Oral MRL

Information on the toxicity of hydrogen sulfide following oral exposure is limited to a dietary exposure study in pigs (Wetterau et al. 1964). The observed effects include a 23% decrease in body weight gain at 6.7 mg/kg/day in pigs exposed for 105 days and diarrheic digestive disturbance in pigs exposed to 15 mg/kg/day for a few days. Interpretation of this study is limited because very few details are reported, (e.g., no information on strain, methods used, number of animals studied, or statistics). This study was considered inadequate for MRL derivation.

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of hydrogen sulfide. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is

considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for hydrogen sulfide. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

3.2.1.1 Death

There have been numerous case reports of human deaths after acute exposure to presumably high concentrations (≥500 ppm) of hydrogen sulfide gas (Beauchamp et al. 1984). NIOSH (1977a) reported that hydrogen sulfide was the primary occupational cause of unexpected death. Snyder et al. (1995), summarizing 10 years of data (1983–1992) from the Poison Control Centers National Data Collection system, indicated that at least 29 deaths and 5,563 exposures were attributed to hydrogen sulfide during that time period. Most fatal cases associated with hydrogen sulfide exposure occurred in relatively confined spaces, such as sewers (Adelson and Sunshine 1966), animal processing plants (Breysse 1961), waste dumps (Allyn 1931), sludge plants (NIOSH 1985a), tanks and cesspools (Campanya et al. 1989; Freireich 1946; Hagley and South 1983; Morse et al. 1981; Osbern and Crapo 1981), and other closed environments (Deng and Chang 1987; Parra et al. 1991). Almost all individuals described in these reports lost consciousness quickly after inhalation of hydrogen sulfide, sometimes after only one or two breaths (the so-called "slaughterhouse sledgehammer" effect). Many of the case studies involved accidental poisonings for which the concentrations and/or duration of exposure were not known (Allyn 1931; Arnold et al. 1985; Burnett et al. 1977; Deng and Chang 1987; Freireich 1946; Hagley and South 1983; Morse et al. 1981). In some cases, the victims were exposed for a period of time ranging from a few minutes to an hour and were unable to be revived (Adelson and Sunshine 1966; Deng and Chang 1987; NIOSH 1989; Osbern and Crapo 1981).

Death occurring after acute exposure to hydrogen sulfide appears to be the result of respiratory failure or arrest, with most cases initially presenting with respiratory insufficiency, noncardiogenic pulmonary edema, coma, and cyanosis. Three men lost consciousness and died after entering a sewer containing high concentrations of hydrogen sulfide; all had the characteristic odor of hydrogen sulfide at autopsy and presented with cyanosis and pulmonary edema (Adelson and Sunshine 1966). After being exposed to hydrogen sulfide in a bathroom connected to a manure pit, a man developed nausea, vomiting, dizziness, and dyspnea, and died a few hours later; hemorrhagic bronchitis and asphyxiation were noted as the cause of death (Parra et al. 1991).

Estimates of hydrogen sulfide exposure were available for some of the cases reported involving deaths. After developing decerebrate responses to painful stimuli and partial seizures, with subsequent indications of brain stem damage, a 16-year-old boy died (Hagley and South 1983). He was exposed to what was presumed to be hydrogen sulfide in a liquid manure tank; 2 weeks after exposure, hydrogen sulfide

concentrations measured 30 cm below the tank manhole were >150 ppm, the detection limit of the equipment. In another incident, a 16-year-old boy was 10 meters away from an underground liquid manure storage tank, the contents of which had been agitating for 30–60 minutes; he began coughing, vomited, lost consciousness, and died (Morse et al. 1981). Autopsy showed tracheobronchial aspiration of stomach contents, focal pulmonary hemorrhages and edema, and small petechial brain hemorrhages. Hydrogen sulfide concentrations were found to be >60 ppm (equipment detection limit) under similar conditions in the vicinity of the accident 2 days later. Although some other gases common to this environment were not detected, it is possible that there was simultaneous exposure to other compounds. A boy and his father were overcome and died after inhaling hydrogen sulfide gas from a discarded drum at a manufacturing dump (Allyn 1931). Although the concentration of the gas inside the drum at the time of exposure was not known, a crude attempt was made to estimate exposure. Gas was collected from the drum 2 weeks after the accident and diluted 1:400 with air. A rat exposed to this dilution died after 40 seconds of exposure.

Three of five men, who lost consciousness within a few minutes of entering a partially drained underground liquid manure storage tank, died before reaching the hospital; autopsy showed that two had massive liquid manure pulmonary aspiration, while the third had fulminant pulmonary edema without manure aspiration (Osbern and Crapo 1981). Markedly elevated heart-blood sulfide-ion levels indicated significant hydrogen sulfide exposure. Air samples analyzed about a week after the accident detected only 76 ppm of hydrogen sulfide, but the study authors noted that the environmental conditions were probably different (e.g., warmer weather, less-concentrated manure).

Two maintenance workers at an animal tanning company collapsed and died no more than 45 minutes after entering a sewer manhole; a hydrogen sulfide concentration of 200 ppm was obtained just inside the manhole 6 days after the accident (NIOSH 1989). A worker at a poultry feather processing plant died after being exposed to hydrogen sulfide gas for an estimated 15–20 minutes (Breysse 1961). Testing performed later in the area where the exposure occurred indicated that hydrogen sulfide concentrations ranged from 2,000 to 4,000 ppm. Pulmonary, intracranial, and cerebral edema and cyanosis were noted at autopsy.

Claims for acute hydrogen sulfide exposure that occurred over a 5-year period (1969–1973) in Alberta, Canada, primarily among petrochemical workers, were reviewed by Burnett et al. (1977). Acute effects noted included coma, disequilibrium, and respiratory insufficiency with pulmonary edema. Of 221 cases, there were 14 deaths. A follow-up study of 250 workers' claims for hydrogen sulfide exposure from 1979

to 1983 in Alberta, Canada, found 7 fatalities that usually involved the central nervous and respiratory systems; hepatic congestion and cardiac petechiae were also noted (Arnold et al. 1985). The difference in fatality rate (6% down to 2.8%) was attributed to improved first aid training and an increased awareness of the dangers of hydrogen sulfide.

Only very limited information is available on mortality in humans associated with chronic exposure to hydrogen sulfide. Bates et al. (1997), taking advantage of the fact that the New Zealand city of Rotorua is in a geothermally active area, conducted a retrospective ecological epidemiologic study in which they compared the mortality for selected diseases between residents in Rotorua and the rest of New Zealand. Rotorua uses geothermal energy for industrial and domestic heating purposes. Monitoring during the 1970s found levels of hydrogen sulfide as high as 1 mg/m^3 (710 ppb); the most reliable data provided a median concentration of 20 $\mu g/m^3$ (14 ppb) with 35% of the measurements of 70 $\mu g/m^3$ (50 ppb), and 10% over 400 $\mu g/m^3$ (284 ppb). Mortality data examined were limited to the main organ systems known to be at risk in hydrogen sulfide exposure (i.e., the nervous, respiratory and cardiovascular/circulatory systems, and birth defects). Among these four mortality categories, only deaths due to diseases of the respiratory system showed a significantly elevated standardized mortality ratio (SMR=1.18; $p<0.001$). Because the population in the Rotorua area has markedly more Maori than in the rest of New Zealand, and because Maori disease and mortality rates are relatively high compared with those of the non-Maori population, further analysis was carried out with an adjustment for ethnicity. When these data were stratified by sex and ethnicity, female Maoris had an SMR of 1.61 ($p<0.001$). Carrying the analysis to minor groupings of disease, significant increases in SMR were found for rheumatic fever and chronic rheumatic heart disease (SMR=1.51; $p=0.01$), hypertensive disease (SMR=1.61; $p<0.001$), pneumonia and influenza (SMR=1.20; $p=0.008$), and chronic obstructive respiratory disease and allied conditions (SMR=1.20; $p=0.004$). In their analysis of the data, the authors note the numerous issues that can be raised with regard to ecologic studies such as theirs; the two principal issues being confounded by other exposures (e.g., smoking) and by ethnicity misclassification. Despite the fact that the data indicate significant increases in SMRs, the study authors concluded that “no convincing evidence was found in this study of elevated rates of mortality in Rotorua compared with the rest of New Zealand.” They caveat this conclusion with three considerations: not all causes of deaths were considered, exposures were inadequately characterized, and ethnicity misclassification could have obscured important causes of mortality.

Studies performed using laboratory animals exposed to high concentrations of hydrogen sulfide gas have yielded results similar to those observed in humans exposed at high levels. Exposure of Sprague-Dawley

rats to 1,655 ppm killed all five animals within 3 minutes (Lopez et al. 1989). All male F-344 rats exposed to 500–700 ppm hydrogen sulfide gas for 4 hours died, while no rats died when exposed to concentrations up to 400 ppm under these conditions (Khan et al. 1990; Lopez et al. 1987, 1988a, 1988b). Ten of 10 male Wistar rats died after a 12-minute exposure (mean) to 800 ppm hydrogen sulfide (Beck et al. 1979). Concentrations of 335–587 ppm that cause death in 50% of the animals tested (LC_{50}) have been reported in Sprague-Dawley, F-344, and Long Evans rats exposed to hydrogen sulfide gas for 2–6-hour periods (Prior et al. 1988; Tansy et al. 1981), although there were fewer deaths in approximately the same dose range in another study using F-344 rats (Prior et al. 1990). No mortality was reported when male Wistar rats were exposed to up to 500 ppm hydrogen sulfide for 2 hours (Higuchi and Fukamachi 1977).

No deaths occurred among 30 adult female CB-20 mice exposed to 100 ppm hydrogen sulfide for 2 hours/day for 1 day (Elovaara et al. 1978), nor in 20 adult female NMRI mice exposed for 1–4 days (Savolainen et al. 1980). All six mice exposed to 722 ppm hydrogen sulfide for 50 minutes died, while 1,872 ppm hydrogen sulfide killed a group of six mice in 10 minutes (Smith and Gosselin 1964). Five Japanese white rabbits died within 30 minutes of exposure to 500–1,000 ppm hydrogen sulfide (Kage et al. 1992).

No mortality was noted during 90-day studies in which male and female F-344 or Sprague-Dawley rats were exposed for 6 hours/day, 5 days/week, to up to 80 ppm hydrogen sulfide (CIIT 1983b, 1983c). Similar results were obtained at the same concentrations and conditions in a companion study using $B6C3F_1$ mice; although two high-dose animals were killed *in extremis*, and two control animals were found dead in the cage (CIIT 1983a).

All reliable LOAEL values for death in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

The highest NOAEL and all reliable LOAEL values for systemic effects in each species and duration are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. With acute accidental hydrogen sulfide exposure, numerous respiratory effects are observed. Death usually occurs after respiratory distress or arrest from the disruption of oxidative

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat (Wistar)	12 min				800 M (10/10 died)	Beck et al. 1979
2	Rat (Fischer- 344)	4 hr				500 M (4-6 used; all died)	Khan et al. 1990
3	Rat (Sprague-Dawley)	3 min				1655 M (5/5 died)	Lopez et al. 1989
4	Rat (Sprague-Dawley, Fischer-344, Long Evans)	2 hr				587 (LC50)	Prior et al. 1988
5	Rat (Sprague-Dawley, Fischer-344, Long Evans)	4 hr				501 (LC50)	Prior et al. 1988

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
6	Rat (Sprague-Dawley, Fischer-344, Long Evans)	6 hr				335 (LC50)	Prior et al. 1988
7	Rat (Fischer- 344)	4 hr				375 M (2/12 died)	Prior et al. 1990
8	Rat (Sprague-Dawley)	4 hr				444 (LC50)	Tansy et al. 1981
9	Mouse (CD-1)	50 min				722 F (6/6 died)	Smith and Gosselin 1964
10	Rabbit (Japanese white)	14-30 min				500 (5/5 died)	Kage et al. 1992

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	Systemic						
11	Human	>16 min	Resp	5 M			Bhambhani and Singh 1991
			Cardio	5 M			
			Metab	2 M	5 M (increased blood lactate during exercise)		
12	Human	15 min	Resp	10			Bhambhani et al. 1996
13	Human	30 min	Resp	5			Bhambhani et al. 1994
			Cardio	5			
14	Human	2x 30 min	Musc/skel		5 M (decrease in citrate synthase when exercising at 50% maximum aerobic power)		Bhambhani et al. 1996b

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
15	Human	2x30 min	Cardio	10			Bhambhani et al. 1997
			Metab		10 (increase in blood lactate and decrease in oxygen uptake)		
16	Human	30 min	Resp		2[b] (increased airway resistance and decreased specific airway conductance in 2/10 asthmatics)		Jappinen et al. 1990
17	Rat (Sprague-Dawley)	3 hr	Resp	80 M	200 M (necrosis of olfactory epithelium and regeneration of respiratory epithelium in nose)		Brenneman et al. 2002
18	Rat (Sprague-Dawley)	3 hr 5 d	Resp	30 M	80 M (necrosis of nasal olfactory epithelium in 5/5 rats)		Brenneman et al. 2002

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
19	Rat (Fischer- 344)	4 hr	Resp		200 M (increase in protein and lactate dehydrogenase in lavage fluid; focal areas of perivascular edema; proteinaceous material in the alveoli)		Green et al. 1991
20	Rat (Wistar)	1 hr	Resp		100 M (increased respiration rate)		Higuchi and Fukamachi 1977
			Cardio		100 M (increased blood pressure, heart rate)		
21	Rat (Fischer- 344)	4 hr	Resp	10 M	50 M (15% reduction in lung cytochrome c oxidase activity)		Khan et al. 1990
22	Rat (Fischer- 344)	4 hr	Resp	50 M	200 M (decreased respiratory rate of pulmonary alveolar macrophages stimulated with zymosan)		Khan et al. 1991

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form
					Less Serious (ppm)	Serious (ppm)	
23	Rat (Wistar)	20-60 min	Resp		75 M (slight congestion)		Kohno et al. 1991
			Cardio			75 M (cardiac arrhythmia; decreased heart rate)	
24	Rat (Fischer- 344)	4 hr	Resp		10 M (increased cellularity in nasal lavage fluid)		Lopez et al. 1987
25	Rat (Fischer- 344)	4 hr	Resp		83 M (mild perivascular edema)		Lopez et al. 1988a
26	Rat (Fischer- 344)	4 hr	Resp			400 M (severe inflammation and necrosis of respiratory and olfactory epithelium)	Lopez et al. 1988b
27	Rat (Fischer- 344)	4 hr	Ocular	200 M	400 M (epiphora)		Lopez et al. 1988b
28	Rat (Fischer- 344)	4 hr	Resp			375 M (moderate to massive pulmonary edema)	Prior et al. 1990

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
29	Gn Pig (NS)	11 d 1 hr/d	Ocular		20 M (eye irritation)		Haider et al. 1980
30	Rabbit (mixed breeds)	1.5 hr or 5 d 0.5hr/d	Cardio			72 (changes in ventricular repolarization; cardiac arrhythmia)	Kosmider et al. 1967
	Immuno/ Lymphoret						
31	Rat (Fischer- 344)	4 hr		50 M	200 M (decreased respiratory rate of pulmonary alveolar macrophages stimulated with zymosan)		Khan et al. 1991
	Neurological						
32	Human	30 min			2 (headache in 3/10 asthmatics)		Jappinen et al. 1990
33	Rat (Wistar)	20 min				800 M (unconsciousness)	Beck et al. 1979
34	Rat (Wistar)	2 hr		100 M	200 M (decreased response rate in conditioned avoidance task)		Higuchi and Fukamachi 1977

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
35	Rat (Fischer- 344)	4 hr		200 M	400 M (lethargy)		Lopez et al. 1988b
36	Rat (CD)	3 hr/d 5 d		30 M	80 M (decreased spontaneous motor activity)		Struve et al. 2001
37	Gn Pig (NS)	11 d 1 hr/d			20 M (decreased cerebral hemisphere and brain stem total lipids and phospholipids)		Haider et al. 1980
38	Rabbit (mixed breeds)	1.5 hr				72 (unconsciousness)	Kosmider et al. 1967
	INTERMEDIATE EXPOSURE						
	Systemic						
39	Rat (Sprague-Dawley)	6 hr/d 7 d/wk 10 wk	Resp	10[c] M	30 M (olfactory neuron loss and basal cell hyperplasia in nasal olfactory epithelium)		Brenneman et al. 2000

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
40	Rat (Fischer- 344)	90 d 5 d/wk 6 hr/d	Resp	10	30 (olfactory neuron loss in the nasal olfactory epithelium)		CIIT 1983b
			Cardio	80			
			Gastro	80			
			Hemato	80			
			Musc/skel	80			
			Hepatic	80			
			Renal	80			
			Endocr	80			
			Dermal	80			
			Ocular	80			
			Bd Wt	80			

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
41	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d	Resp	10	30 (olfactory neuron loss in the nasal olfactory epithelium and bronchiolar epithelial hyperplasia)		CIIT 1983c
			Cardio	80			
			Gastro	80			
			Hemato	80			
			Musc/skel	80			
			Hepatic	80			
			Renal	80			
			Endocr	80			
			Dermal	80			
			Ocular	80			
			Bd Wt	80 M 30.5 F[d]	80 F (10% decrease in body weight)		

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
42	Rat (Sprague-Dawley)	gd 1-ppd 21 7 hr/d	Metab		20 F (50% increase in circulating glucose levels in dams)		Hayden et al. 1990a
43	Rat (Sprague-Dawley)	gd 6-ppd 21 7 hr/d	Hepatic	50 F	75 F (increased maternal liver cholesterol levels)		Hayden et al. 1990b
44	Rat (Sprague-Dawley)	gd 6-20 6 hr/d	Bd Wt	100 F	150 F (pregnant rats lost weight)		Saillenfait et al. 1989

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)	Reference Chemical Form
45	Mouse (B6C3F1)	90d 5 d/wk 6 hr/d	Resp	10	80	(inflammation of nasal mucosa)		CIIT 1983a
					30	(olfactory neuron loss in the nasal olfactory epithelium)		
			Cardio	80				
			Gastro	80				
			Hemato	80				
			Musc/skel	80				
			Hepatic	80				
			Renal	80				
			Endocr	80				
			Dermal	80				
			Ocular	80				
			Bd Wt	30.5	80	(7-14% decrease in body weight)		

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
46	Pig (Crossbred)	17 d 24 hr/d	Resp	8.5			Curtis et al. 1975
			Gastro	8.5			
			Hepatic	8.5			
			Renal	8.5			
			Ocular	8.5			
			Bd Wt	8.5			
	Immuno/ Lymphoret						
47	Rat (Fischer- 344)	90 d 5 d/wk 6 hr/d		80			CIIT 1983b
48	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d		80			CIIT 1983c
49	Mouse (B6C3F1)	90d 5 d/wk 6 hr/d		80			CIIT 1983a

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	Neurological						
50	Rat (Fischer- 344)	90d 5 d/wk 6 hr/d		80			CIIT 1983b
51	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d		30.5 M[d] 80 F	80 M (5% decrease in brain weight)		CIIT 1983c
52	Rat (Sprague-Dawley)	25 wk 5 d/wk		50 M			Gagnaire et al. 1986
53	Rat (Sprague-Dawley)	4 hours/day 5 days/week 5-11 weeks			125 M (impaired learning of new tasks on a radial arm maze)		Partlo et al. 2001
54	Mouse (B6C3F1)	90d 5 d/wk 6 hr/d		80			CIIT 1983a
	Reproductive						
55	Rat (Fischer- 344)	90d 5 d/wk 6 hr/d		80			CIIT 1983b

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
56	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d		80			CIIT 1983c
57	Rat (Sprague-Dawley)	6 hr/d 7 d/wk 60-70 d		80			Dorman et al. 2000
58	Mouse (B6C3F1)	90d 5 d/wk 6 hr/d		80			CIIT 1983a
	Developmental						
59	Rat (Sprague-Dawley)	6 hr/d 7 d/wk 60-70 d		80			Dorman et al. 2000
60	Rat (Sprague-Dawley)	gd 5-ppd 21 7 hr/d			20 F (severe alterations in architecture and growth characteristics of Purkinje cell dendritic fields which may be indicative of neurotoxicity)		Hannah and Roth 1991
61	Rat (Sprague-Dawley)	gd 5-ppd 21 7 hr/d		50	75 (decreases in brain amino acid levels of pups)		Hannah et al. 1989, 1990

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
62	Rat (Sprague-Dawley)	gd 1-ppd 21 7 hr/d		75 F			Hayden et al. 1990a
63	Rat (Sprague-Dawley)	gd 6-ppd 21 7 hr/d		75 F			Hayden et al. 1990b
64	Rat (Sprague-Dawley)	gd 6-20 6 hr/d		150 F			Saillenfait et al. 1989
65	Rat (Sprague-Dawley)	gd 5-ppd 21 7 hr/d			20 F (decreases in norepinephrine in the frontal cortex, increase in serotonin in the frontal cortex of pups)		Skrajny et al. 1992

a The number corresponds to entries in Figure 3-1.

b Used to derive an acute-duration Minimal Risk Level (MRL) of 0.2 ppm; concentration divided by an uncertainty factor of 9 (3 for use of a minimal LOAEL, and 3 for human variability).

c Used to derive an intermediate-duration Minimal Risk Level (MRL) of 0.02 ppm; the NOAEL was adjusted for intermittent exposure and multiplied by the regional gas dose ratio (RGDR) for extrathoracic effects to calculate a human equivalent concentration (HEC). The MRL was obtained by dividing the NOAEL(HEC) by an uncertainty factor of 30 (3 for extrapolation from animals to humans with a dosimetric adjustment and 10 for human variability)

d Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-1. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

B = both; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = Female; Gastro = gastrointestinal; gd = gestational day; hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; metab = metabolism; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; ppd = post-partum day; Resp = respiratory; wk = week(s)

Figure 3-1. Levels of Significant Exposure to Hydrogen Sulfide - Inhalation

Acute (≤14 days)

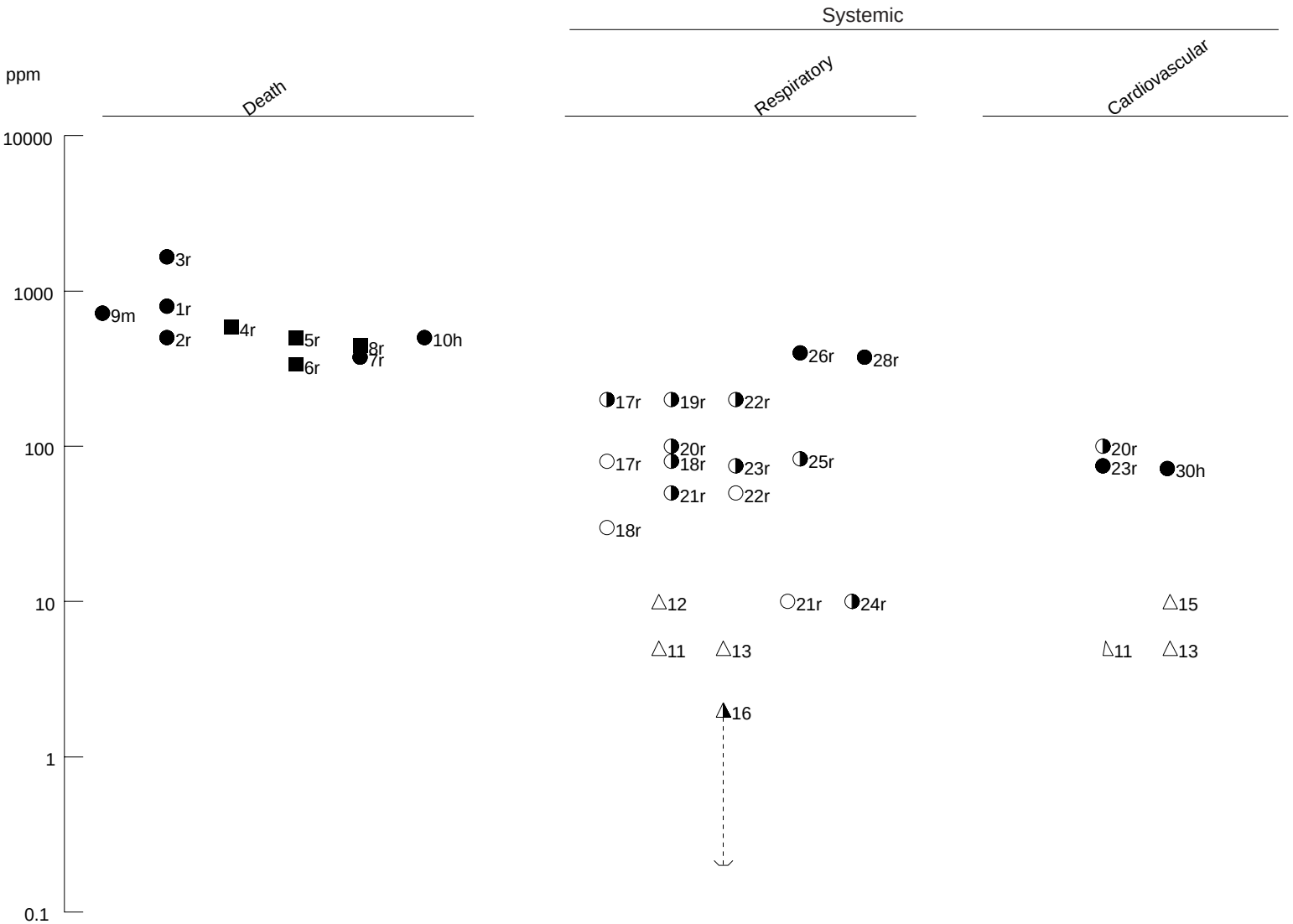


Figure 3-1. Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (*Continued*)

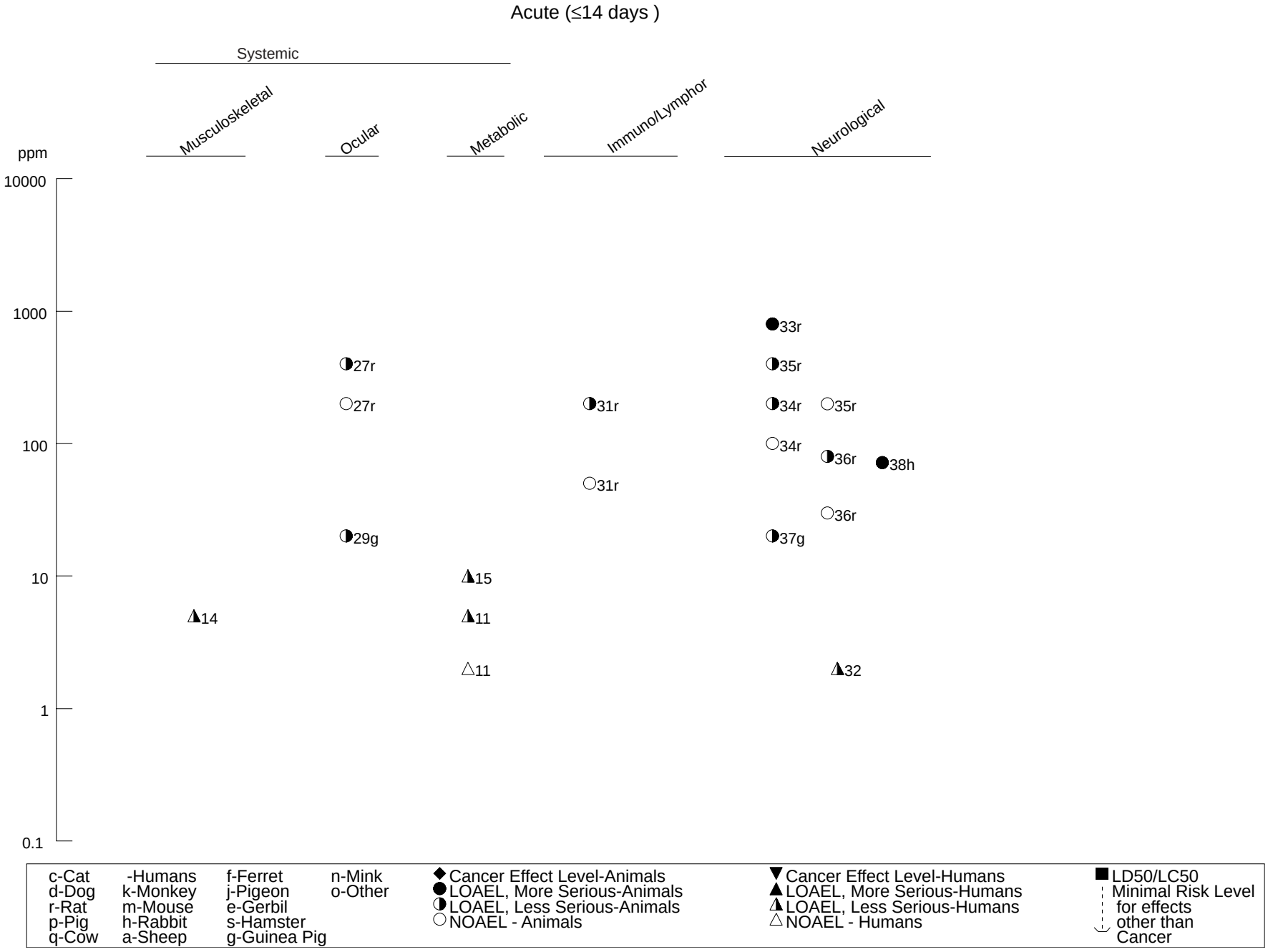


Figure 3-1. Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (*Continued*)

Intermediate (15-364 days)

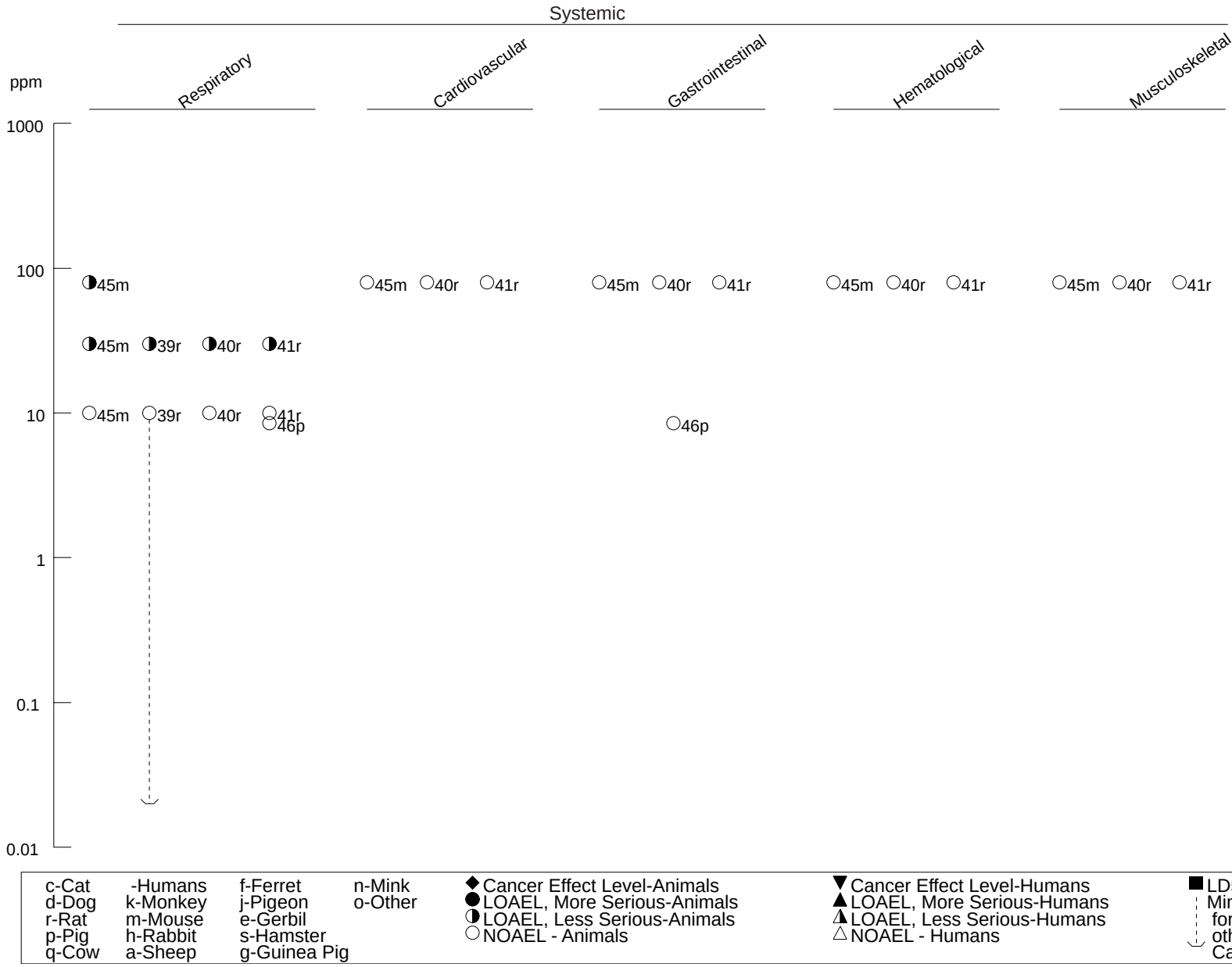


Figure 3-1. Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (*Continued*)

Intermediate (15-364 days)

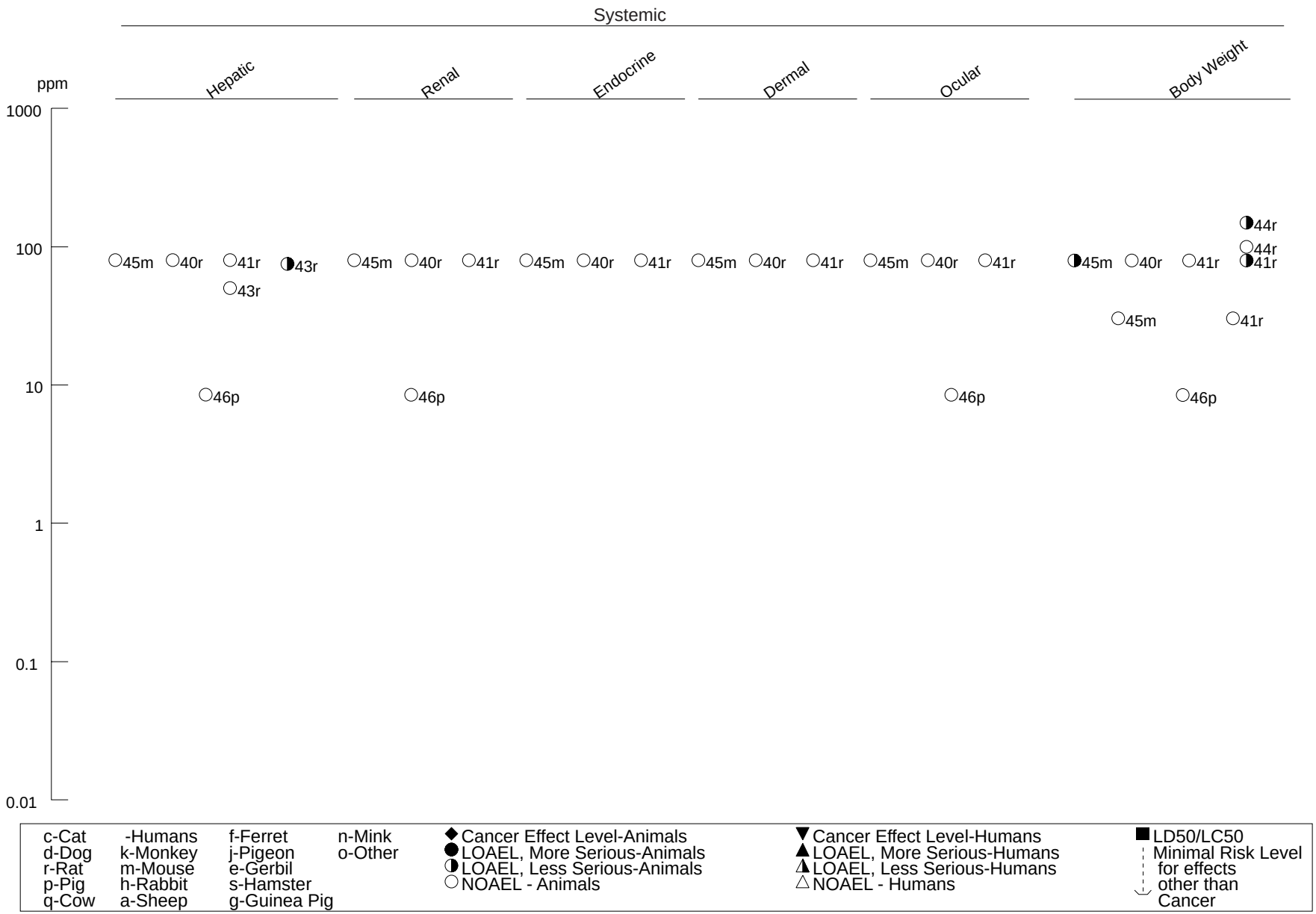
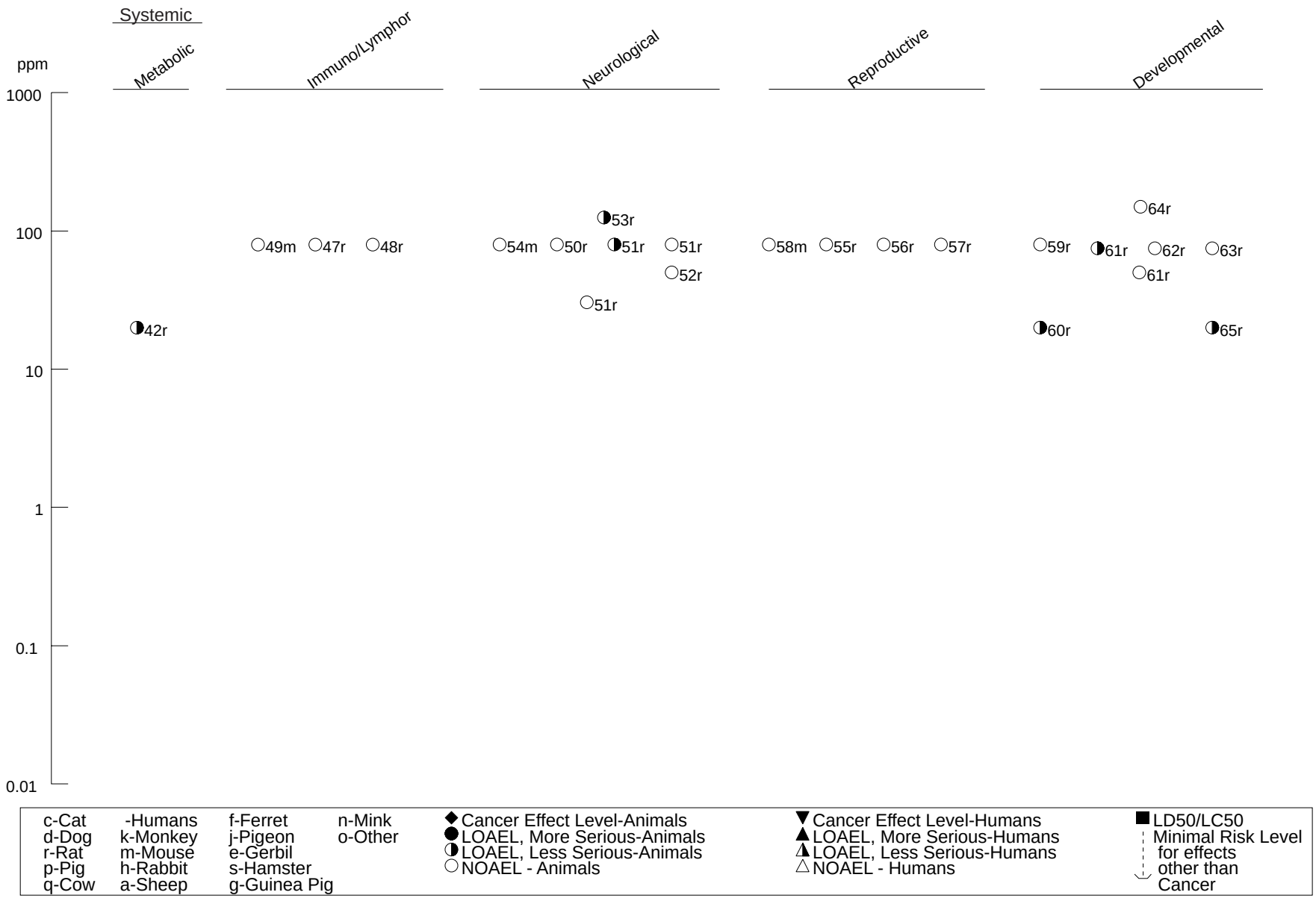


Figure 3-1. Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (*Continued*)

Intermediate (15-364 days)



metabolism in the brain. Respiratory distress has also been noted in individuals who survived after acute exposures (Osbern and Crapo 1981; Peters 1981; Spolyar 1951). Other respiratory effects of acute hydrogen sulfide exposure include noncardiogenic pulmonary edema (Arnold et al. 1985; Burnett et al. 1977; Deng and Chang 1987; Thoman 1969; Tvedt et al. 1991a, 1991b), sore throat, cough (Burnett et al. 1977; Jaakkola et al. 1990), and dyspnea (Arnold et al. 1985; Burnett et al. 1977; Krekel 1964; Osbern and Crapo 1981; Parra et al. 1991; Ravizza et al. 1982; Stine et al. 1976; Thoman 1969). Cyanosis has been reported in a number of case reports and is believed to result from respiratory distress (Arnold et al. 1985; Tvedt et al. 1991a, 1991b). In most studies, exposure concentrations and/or durations were unknown. Among hydrogen sulfide exposure survivors, respiratory symptoms generally subsided within several weeks of exposure, but occasionally persisted for several months or longer (Duong et al. 2001; Parra et al. 1991). Acute exposure to >500 ppm hydrogen sulfide is considered to cause rapid respiratory failure (Beauchamp et al. 1984).

Respiratory distress was noted in two workers exposed to >40 ppm hydrogen sulfide for <25 minutes (Spolyar 1951). Bhambhani and associates have conducted a number of studies of young healthy volunteers exposed to hydrogen sulfide via oral inhalation. Male volunteers were exposed to hydrogen sulfide concentrations up to 5 ppm for more than 16 minutes after graded exercise that was performed to exhaustion (Bhambhani and Singh 1991). No effects on expired ventilation or maximum power output were noted, but exposure to 5 ppm resulted in a significant increase in maximum oxygen uptake compared to controls. At exposures to 2 and 5 ppm, the respiratory exchange ratio was decreased significantly compared to controls. The study authors attributed this to a nonsignificant trend toward increased oxygen uptake and decreased carbon dioxide output compared to controls (Bhambhani and Singh 1991). Another study examined the effects of inhalation of 5 ppm hydrogen sulfide on respiratory physiological parameters and found no changes in partial pressure of oxygen, partial pressure of carbon dioxide, oxygen uptake (VO_2), percentage of oxygen uptake (VO_2%), uptake of carbon dioxide (VCO_2) and V_E, or respiratory exchange ratio in male or female volunteers during 30 minutes of submaximal exercise (Bhambhani et al. 1994). A third study found that inhalation of 10 ppm of hydrogen sulfide for 15 minutes at elevated metabolic and ventilation rates did not result in significantly altered pulmonary function test results in men and women (Bhambhani et al. 1996a). It should be noted that the subjects were unable to smell the hydrogen sulfide and their eyes were not exposed to the gas.

Pulmonary function tests were performed on persons with asthma exposed to 2 ppm of hydrogen sulfide for 30 minutes in a sealed chamber (Jappinen et al. 1990). Although no significant changes were noted in airway resistance or specific airway conductance as a group, 2 of 10 subjects showed changes in excess of

30% in both airway resistance and specific airway conductance, an indication of bronchial obstruction (Jappinen et al. 1990). No statistically significant changes were noted in forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and forced expiratory flow (Jappinen et al. 1990). Pulmonary function was unaffected following the same exposure protocol in 26 male pulp mill workers who had previously had daily hydrogen sulfide exposures, usually to <10 ppm (Jappinen et al. 1990). No significant changes were noted in FVC, FEV_1, or bronchial responsiveness to histamine challenge in this group of workers, which included subgroups of smokers, workers with previous allergies, and atrophic individuals. Findings in this study are similar to those observed in Bhambhani et al. (1996a).

Hessel et al. (1997) examined the pulmonary health effects of hydrogen sulfide exposure in a group of Canadian oil and gas workers. Exposure to hydrogen sulfide was assessed by questionnaire as was the occurrence of respiratory symptoms; in addition, smoking and occupational histories were conducted. Lung health was assessed via spirometric testing and by skin prick testing for six common antigens. The workers were divided into three exposure groups: none, gas exposure (sufficient to produce symptoms), and knockdown (exposure sufficient to cause unconsciousness). None of the lung function indicators (FEV_1, FVC, or FEV_1/FVC) differed significantly among the three groups. Significantly increased odds ratios (ORs) were seen only in those in the knockdown group who showed significant excesses for several symptoms, including: shortness of breath (OR=3.55; 95% confidence interval [CI]=1.02–12.4); wheeze with chest tightness (OR=5.15; 95% CI=1.29–20.6); and attacks of wheeze (OR=5.08; 95% CI=1.28–20.6).

In a cross-sectional study of sewer and water treatment workers, Richardson (1995) evaluated the association of hydrogen sulfide exposures to reduced lung function using spirometric testing. Job titles were used to categorize sewer workers into high, medium, and low exposure groups; however, there was no quantification of hydrogen sulfide levels. Water treatment workers who were not occupationally exposed to hydrogen sulfide were chosen as a comparison group. Findings included significant differences between spirometric values (FEV_1/FVC) of sewer and water treatment workers across a number of age strata, irrespective of smoking status, although smoking status reduced the impact somewhat. When stratified by presumed exposure to hydrogen sulfide, only those sewer workers with presumed high exposure showed a significant difference from water workers, although a dose-related trend in lung function at both medium and high exposures was observed. In addition, the prevalence OR for obstructive lung disease was 21.0 (95% CI=2.4–237.8) in nonsmoking sewer workers with presumed high hydrogen sulfide exposure when compared to nonsmoking water treatment workers. The prevalence

odds ratio for sewer workers who smoke versus water treatment workers who smoke was 1.7 (95% CI=0.2–13.6).

In a report comparing community responses to low-level exposure to a mixture of air pollutants from pulp mills, Jaakkola et al. (1990) reported significant differences in respiratory symptoms between polluted and unpolluted communities. The pollutant mixture associated with the pulp mills included particulates, sulfur dioxide, and a series of 'malodorous sulfur compounds.' Major contributors in the latter mixture include hydrogen sulfide, methyl mercaptan, and methyl sulfides. In this study, the responses of populations from three communities (a nonpolluted community, a moderately polluted community, and a severely polluted community were compared). Initial exposure estimates were derived from dispersion modeling; these estimates were subsequently confirmed with measurements taken from monitoring stations located in the two polluted communities. These measurements indicated that both the mean and the maximum 4-hour concentrations of hydrogen sulfide were higher in the more severely polluted community (4 and 56 μg/m^3; 2.9 and 40 ppb) than in the moderately polluted one (2 and 22 μg/m^3; 1.4 and 16 ppb). Particulate measurements made concurrently, and sulfur dioxide measurements made subsequently, showed a similar difference in the concentrations of these two pollutants between the two polluted communities. A cross-sectional, self-administered questionnaire was used to gather data on the occurrence (i.e., often or constantly) of a variety of symptoms and effects during two time periods (the past 4 weeks and the previous 12 months). Respiratory end points evaluated included cough, nasal symptoms, breathlessness or wheezing, numbers of respiratory infections, history of asthma, and chronic respiratory diseases. The occurrence of nasal symptoms and cough was found to be significantly greater in the subjects living in the two polluted communities when compared to those in the nonpolluted community. Breathlessness or wheezing was also increased, although not to the level of significance. All three of these end points showed a dose-related increase; that is, the greatest occurrence of symptoms occurred in the more highly-polluted community, followed by the less polluted, and then the nonpolluted communities. Because of the mixed exposures, however, the role of hydrogen sulfide in these effects is unclear.

A subsequent report by Marttila et al. (1994b) examined the impact of long-term exposure to the same mixture of malodorous sulfur compounds on children from these same three communities. The findings in children (i.e., nasal symptoms and cough) in the most severely polluted community were similar to those reported above and showed increased risks both for the 4-week and the 12-month intervals, although none of these risks reached statistical significance.

Marttila et al. (1995) also examined the relationship between daily exposure to malodorous sulfur compounds (measured as total reduced sulfur [TRS]) from pulp production and experience of symptoms in a small population living in the vicinity of a pulp mill. The major components of the malodorous sulfur compounds are hydrogen sulfide, methyl mercaptan, and methyl sulfides. This work was initiated due to the observation that an unusually high short-term exposure to malodorous sulfur compounds (maximum 4-hour concentrations of hydrogen sulfide at 135 μg/m^3 [96 ppb]) led to a considerable increase in the occurrence of ocular, respiratory, and neuropsychological symptoms (Haahtela et al. 1992). During the study period, daily mean TRS concentrations varied from 0 to 82 μg/m^3, and monthly mean concentrations varied from 3 to 19 μg/m^3. Following a baseline questionnaire, the study was conducted with six consecutive questionnaires after three predefined levels of exposure to TRS (daily mean <10 μg/m^3, medium exposure 10–30 μg/m^3, high exposure >30 μg/m^3). The study found a dose-related increase in the probability of both nasal (i.e., stuffy or runny nose) and pharyngeal irritation. For nasal symptoms, the probability ratios were 3.13 (95% CI=1.25–7.25) and 8.50 (95% CI=3.19–18.64) for medium and high exposure, respectively. For pharyngeal symptoms, the probability ratios were 2.0 (95% CI=0.92–4.14) and 5.20 (95% CI=1.95–1.99) for the medium and high exposure levels, respectively.

Partti-Pellinen et al. (1996) used a cross-sectional, self-administered questionnaire to assess the eye, respiratory tract, and central nervous system symptoms experienced by adults in a slightly polluted and a reference community. In the polluted community, the mean annual TRS concentrations were 2–3 μg/m^3, the 24-hour average concentrations varied between 0 and 56 μg/m^3, and the maximum 1-hour concentration was 155 μg/m^3; there was no TRS detected in the reference community. In the polluted community, the sulfur dioxide annual mean concentration was 1 μg/m^3, the 24-hour average concentrations varied between 0 and 24 μg/m^3, and the maximum 1-hour concentration was 152 μg/m^3. In the reference community, the mean sulfur dioxide level was 1 μg/m^3 and the maximum 1-hour concentration was 30 μg/m^3.

Symptoms evaluated over the previous 4 weeks and previous 12 months included eye irritation, nasal irritation, cough, breathlessness or wheezing, and headache or migraine. After adjusting for age, sex, smoking, history of allergic diseases, education, and marital status, increased odds ratios were seen for all of these symptoms at both time periods. However, significant increases in odds ratios were seen only for headache or migraine in the previous 4 weeks (OR=1.82; 95% CI=1.06–31.5) and in the past 12 months (OR=1.70; 95% CI=1.05–2.73) and cough in the past 12 months (OR=1.64; 95% CI=1.01–2.64). These findings led the authors to conclude that the adverse health effects of TRS occur at lower concentrations than previously reported. However, these findings are also confounded by daily average levels of TRS as

high as 56 µg/m^3 and by the presence of sulfur dioxide which, though occurring at the same mean annual concentration in the two communities, showed much higher peaks in the polluted community. Furthermore, no information was provided on particulate levels, which could also be important to these findings.

This series of studies (Jaakkola et al. 1990; Haahtela et al. 1992; Marttila et al. 1994a, 1994b, 1995; Partti-Pellinen et al. 1996) report the results of the South Karelia Air Pollution Study, which began in 1986 to evaluate the effects of air pollution on human health and the environment. In the early studies of this series (Haahtela et al. 1992; Jaakkola et al. 1990; Marttila et al. 1994b), levels of hydrogen sulfide, sulfur dioxide, particulates, and methyl mercaptan were individually reported. In the later studies (Marttila et al. 1994a, 1995; Partti-Pellinen et al. 1996), a complex mixture of 'malodorous sulfur components' (that included hydrogen sulfide, methyl mercaptan, and methyl sulfides) was monitored as TRS using a method that first removes any sulfur dioxide, then oxidizes the TRS compounds to sulfur dioxide, and reports the results as µg/m^3 TRS. It is not possible, from the information provided, to determine precisely what proportion of the TRS is actually hydrogen sulfide, although the authors indicate that it is about two-thirds (Marttila et al. 1994b). The fact that in virtually all of these studies, effects were linked to exposures to mixtures, even though hydrogen sulfide appears to have been the dominant sulfur compound, complicates interpretation of these results. It is probably reasonable to conclude that these studies demonstrate that low levels of hydrogen sulfide in combination with other sulfur-containing pollutants, and possibly due to combination with particulates and/or sulfur dioxide, can have an adverse effect on respiratory health. However, it is not possible at this time to determine whether it is the low annual average values of 1–2 µg/m^3 TRS, or the daily average concentrations (56 µg/m^3 TRS) that are associated with these findings.

ATSDR (Campagna et al. 2004) examined the possible relationship between ambient levels of hydrogen sulfide and total reduced sulfur and hospital visits among residents of Dakota City and South Sioux City, Nebraska. Total reduced sulfur is the combined concentrations of hydrogen sulfide, methyl mercaptan, dimethyl sulfide, and dimethyl disulfide; air monitoring data indicate that hydrogen sulfide was the primary constituent of the total reduced sulfur. The primary sources of total reduced sulfur were a beef slaughter facility and a leather tanning facility. Among children under 18 years of age, positive associations were found between hospital visits for all respiratory disease (including asthma) and the high hydrogen sulfide level the previous day and the high levels of total reduced sulfur on the previous day. Positive associations were found between hospital visits for asthma and the previous day's high hydrogen

sulfide level in adults and total reduced sulfur in children. A high total reduced sulfur or hydrogen sulfide level was defined as a 30-minute rolling average of ≥30 ppb.

As discussed in more detail in Section 3.2.1.1, Bates et al. (1997) found a significant increase in mortality from diseases of the respiratory system for residents of the Rotorua area of New Zealand for the period of 1981–1990. Rotorua is in an area of high geothermal activity; sampling from a campaign in 1978 indicated a median concentration for hydrogen sulfide of about 20 μg/m^3 with 35% of the measurements >70 μg/m^3 and 10% of the measurements >400 μg/m^3. Problems with the analysis, however, led these authors to conclude that there were no clear indications of excess mortality. In a follow-up to this study, Bates et al. (2002) used hospital discharge records for 1993–1996 to assess the incidence of respiratory disease; unlike the previous study, exposure was classified as high, medium, or low, based on residence at the time of discharge. A statistically significant ($p<0.001$), exposure-related trend for increased incidence of respiratory disease was found. The incidence of minor respiratory disease groups was also significantly ($p<0.01$) increased. In general, the incidence of respiratory disease was significantly elevated in the high exposure group, but not at lower exposure levels, with the exception of the incidences of other diseases of the upper respiratory tract category, which were increased in all three exposure groups. The standardized incidence ratios (SIRs) (and 95% confidence limits) for this category were 1.48 (1.34–1.63), 1.68 (1.39–2.01), and 1.98 (1.58–2.45) in the low, medium, and high exposure groups, respectively. Limitations in the design of this study, such as lack of exposure monitoring data, lack of data on potential confounding factors (e.g., smoking, differences in socioeconomic status in the different exposure groups), lack of residence history data, and lack of information on potential exposure at work, limit the interpretation of these data.

In addition to an increase in respiration rate that was noted in Wistar rats exposed to 100–200 ppm hydrogen sulfide for 1 hour (Higuchi and Fukamachi 1977), a number of histological and biochemical changes have been noted in the respiratory tissues and fluids of animals acutely exposed to hydrogen sulfide. Cytotoxicity to both nasal or bronchioalveolar lavage and pulmonary cells was demonstrated in a study of male F-344 rats exposed to 0, 10, 200, or 400 ppm hydrogen sulfide for 4 hours and examined at 1, 20, or 44 hours postexposure (Lopez et al. 1987). Cellularity of nasal lavage fluid was increased at all exposure concentrations, because of either exfoliation of degenerated epithelial cells at 1 hour, or exudation of polymorphonuclear leukocytes (PMNs) at 20 hours postexposure, which served as an indicator of cell damage. Altered pulmonary vascular permeability was indicated by increased protein in nasal lavage fluids in animals exposed to airborne concentrations of 400 ppm, but this condition resolved by 20 hours postexposure. Increased lactate dehydrogenase activity (at exposure levels of 200 and

400 ppm) and alkaline phosphatase activity (with exposure to 400 ppm) in bronchoalveolar lavage fluid observed in this study were indicative of toxic effects on the pulmonary epithelium. In addition, pulmonary alveolar macrophages from animals exposed by inhalation to airborne concentrations of 200 or 400 ppm hydrogen sulfide had some increase in cytoplasmic vacuolation, but the bronchoalveolar epithelium did not show signs of cellular degeneration or ciliocytophthoria (Lopez et al. 1987).

In similar experiments, Green and co-workers (1991) exposed male F-344 rats to 200 and 300 ppm hydrogen sulfide for 4 hours, and evaluated the impact on lung lavage fluid surface tension, protein concentrations, and lactate dehydrogenase activity. These authors found significant increases in protein concentrations and lactate dehydrogenase activity at both exposure concentrations, but a significant change in the surface tension of lavage fluids only at the high dose. Focal area of perivascular edema and proteinaceous material in the alveoli were also seen in the lungs of the exposed animals.

Histopathological changes have been reported in the nasal cavity of F-344 rats (Lopez et al. 1988b). Male rats were exposed to 0, 10, 200, or 400 ppm hydrogen sulfide for 4 hours. Necrosis and exfoliation of the respiratory and olfactory mucosal cells were observed 1 hour postexposure at concentrations >200 ppm; by 20 hours postexposure, the respiratory epithelium was covered by a layer of deeply basophilic cells containing mitotic figures and severe inflammatory response was noted. The necrosis ultimately ulcerated the respiratory epithelium, causing exposure of the basement membrane (Lopez et al. 1988b). Although some histological changes were observed at 10 and 200 ppm hydrogen sulfide, no dose response was evident; it appears that a concentration >200 ppm is necessary to induce these lesions (Lopez et al. 1988b).

Similarly, Brenneman et al. (2002) observed bilateral symmetrical mucosal necrosis in the nasal olfactory epithelium and respiratory epithelial regeneration in rats exposed to 200 or 400 ppm hydrogen sulfide for 3 hours; the NOAEL for these effects is 80 ppm. However, the respiratory epithelial was not adversely affected in rats similarly exposed 3 hours/day for 5 days (Brenneman et al. 2002). In these rats, necrotic olfactory epithelium and hyperplastic basal cells were observed in rats exposed to 80, 200, or 400 ppm, but not at 30 ppm. A partial regeneration of the olfactory epithelium was observed 2 weeks after exposure termination and a complete regeneration was observed 6 weeks post-exposure.

Cytochrome *c* oxidase activity in lung mitochondria of F-344 rats was significantly decreased at 50 ppm (15%), 200 ppm (43%), and 400 ppm (68%) hydrogen sulfide compared to controls after a 4-hour exposure (Khan et al. 1990). Cytochrome *c* oxidase activity had returned to normal for animals exposed

to 200 ppm, but not for those exposed to 400 ppm, by 24 hours postexposure. Succinate oxidase activity was reduced at 200 ppm (40%) and 400 ppm (63%), but was not affected at 50 ppm (Khan et al. 1990). A 5-week exposure to 10 or 100 ppm hydrogen sulfide (8 hours/day, 5 days/week) also resulted in significant decreases in cytochrome oxidase activity in lung mitochondria (Khan et al. 1998); exposure to 1 ppm did not result in significant alterations.

Significant decreases in numbers of viable pulmonary alveolar macrophages were noted in the lung lavage fluid of male rats exposed for 4 hours to 400 ppm hydrogen sulfide (Khan et al. 1991). This study also showed complete abolition of zymosan-induced stimulation of respiratory rates of pulmonary alveolar macrophages in animals exposed to 200 or 400 ppm. No changes were noted after exposure to 50 ppm hydrogen sulfide.

Histological changes were characterized in the lungs of male F-344 rats exposed to 83 or 439 ppm for 4 hours (Lopez et al. 1988a). At the low dose, mild perivascular edema was found, but at the high dose, numerous changes were observed, including severe but transient pulmonary edema and fibrocellular alveolitis in proximal alveoli; cytoplasmic blebs in the alveolar endothelium; increased numbers of mitotic figures in the bronchiolar epithelium; minor changes in the alveolar epithelium; and necrosis of the ciliated bronchiolar cells. Moderate-to-massive pulmonary edema was evident in male F-344 rats exposed to 375 or 399 ppm for 4 hours (Prior et al. 1990), and slight pulmonary congestion was found in male Wistar rats exposed to 75 ppm hydrogen sulfide for 1 hour (Kohno et al. 1991).

The effects of intermediate-duration exposures to hydrogen sulfide have been examined in rats, mice, and pigs. Respiratory effects were not observed in F-344 (CIIT 1983b) or Sprague-Dawley (CIIT 1983c) rats exposed to hydrogen sulfide at concentrations up to 80 ppm 6 hours/day, 5 days/week, for 90 days. However, a re-examination of the histologic specimens from this study (Dorman et al. 2004) found significant increases in the incidence of olfactory neuron loss in Sprague-Dawley and F-344 rats exposed to 30 or 80 ppm and in male rats exposed to 80 ppm; the no-effect levels in these strains were 10 and 30 ppm, respectively. In addition, increases in the incidence of bronchiolar epithelial hypertrophy and hyperplasia were observed in the female Sprague-Dawley rats exposed to 30 or 80 ppm hydrogen sulfide and in male Sprague-Dawley and F-344 rats exposed to 80 ppm. These findings are similar to those of Brenneman et al. (2000) who found significant increases in the incidence and severity of nasal lesions in male Sprague-Dawley rats exposed to hydrogen sulfide for 6 hours/day, 7 days/week for 10 weeks. The nasal lesions, which were limited to the olfactory mucosa, consisted of multifocal, bilaterally symmetrical olfactory neuron loss, and basal cell hyperplasia. The olfactory neuron loss and basal cell hyperplasia

was found in most animals exposed to 30 or 80 ppm, but was not found in controls or rats exposed to 10 ppm. At 30 ppm, the severity of the olfactory neuron loss and basal cell hyperplasia was graded as mild to moderate. At 80 ppm, the severity of the olfactory neuron loss was moderate to severe and the basal cell hyperplasia was scored as mild.

Inflammation of the nasal mucosa described as minimal to mild rhinitis was observed in $B6C3F_1$ mice exposed to hydrogen sulfide at 80 ppm for 6 hours/day, 5 days/week for 90 days (CIIT 1983a); these lesions were not observed at 30 ppm. A re-examination of the histological specimens from this study, confirmed these results (Dorman et al. 2004) and also found significant increases in the incidence of olfactory neuron loss in the nasal olfactory epithelium of male and female mice exposed to 30 or 80 ppm, but not at 10 ppm.

Three crossbred pigs of unspecified sex were continuously exposed to 0 or 8.5 ppm hydrogen sulfide in inhalation chambers for 17 days (Curtis et al. 1975). No significant changes in body weight gain and no histopathological changes in the respiratory tract (including turbinates, trachea, and lungs) were noted. This study is limited by the number of animals used and because only one exposure concentration was used.

Cardiovascular Effects. Cardiovascular effects have been noted after acute exposures to high concentrations of hydrogen sulfide via inhalation (Arnold et al. 1985). Slight blood pressure increases were noted in several workers exposed to hydrogen sulfide in a pelt room, however, their electro-cardiograms (EKGs) were normal (Audeau et al. 1985). In other instances of hydrogen sulfide poisoning that occurred after a short exposure to high concentrations, no changes in blood pressure were noted despite other cardiac irregularities (Ravizza et al. 1982). Hemodynamic instability was noted in one of two men who survived acute exposure to an unknown concentration of hydrogen sulfide and also swallowed large amounts of manure after entering a partially drained liquid manure pit (Osbern and Crapo 1981). Sinus tachycardia has been noted in men who completely recovered after exposure to hydrogen sulfide (Peters 1981; Ravizza et al. 1982). Supraventricular tachycardia and left bundle block were noted in a worker exposed to hydrogen sulfide generated from a sodium sulfide waste solution dumped onto acid waste material; the effects were temporary (Stine et al. 1976). Extreme tachycardia and hypotension were noted in a woman who attempted to clean a well with muriatic acid and was exposed to an unknown concentration of hydrogen sulfide gas; hypertension was noted in a man exposed during this same incident (Thoman 1969).

EKGs taken on two workers about 2.5 hours after an acute exposure to hydrogen sulfide showed cardiac arrhythmias (Krekel 1964). The workers were exposed for <5 minutes after a spill of sodium sulfide that broke down to release hydrogen sulfide. In one individual, a negative P wave, indicating a substitute rhythm, was noted, while in the other individual, a continuous arrhythmia due to atrial flutter was found. EKGs for both men had returned to normal within 24 hours.

No adverse cardiovascular effects were found when healthy male volunteers were exposed to hydrogen sulfide concentrations up to 5 ppm for more than 16 minutes after graded exercise performed to exhaustion (Bhambhani and Singh 1991). A study that examined the effects of inhalation of 5 ppm hydrogen sulfide on physiological parameters found no changes in heart rate, blood pressure, percent hemoglobin saturation, perceived exertion, or other parameters in healthy male and female volunteers during 30 minutes of submaximal exercise (Bhambhani et al. 1994). A subsequent study examining the effects of inhaling 10 ppm hydrogen sulfide during two 30-minute sessions of submaximal exercise found no significant changes in cardiovascular responses under these conditions (Bhambhani et al. 1997).

In a retrospective epidemiologic study using hospital discharge data from 1981 to 1990, Bates et al. (1998) evaluated the risk of disease to known target organ systems of hydrogen sulfide toxicity in residents of Rotorua, a New Zealand city that uses geothermal energy for industrial and domestic heating purposes. A significant increase in incidence was found for diseases of the circulatory system (SIR=1.05; p=0.001) among Rotorua residents as compared to all other New Zealand residents. Although previous monitoring information from Rotorua in 1978 showed a median concentration of hydrogen sulfide of 20 $\mu g/m^3$, with 35% of the measurements over 70 $\mu g/m^3$ and 10% over 400 $\mu g/m^3$ (Bates et al. 1997), the lack of monitoring information concurrent with these data precludes conclusions with regard to a causal relationship between circulatory system disease and hydrogen sulfide exposures. Using hospital discharge records for 1993–1996, Bates et al. (2002) attempted to examine exposure-related trends for cardiovascular disease among residents of Rotorua. Residents were divided into three exposure categories (low, medium, and high) based on surrogate exposure data. A statistically significant ($p<0.001$) trend for exposure-related increases in the incidence of circulatory system disease was observed. When the circulatory system disease category was further divided into minor disease categories, significant ($p<0.01$) exposure-related trends for cerebrovascular disease and diseases of arteries, arterioles, and capillaries were found. However, no significant increases in SIRs were found for the cerebrovascular disease category. For artery, arteriole, and capillary disease category, the SIRs were significantly elevated for the medium (SIR=1.58, 95% confidence level of 1.17–2.08) and high (SIR=1.66, 95% confidence interval of 1.30–2.09) exposure groups. The lack of exposure data, the

assumption that hydrogen sulfide exposure only occurred at home, and the lack of control for potential confounding factors such as smoking and socioeconomic status limit the interpretation of these data.

Studies in experimental animals have reported EKG alterations (e.g., cardiac arrhythmia) following acute-duration exposure to 72–75 ppm for 1.5 hours or less (Kohno et al. 1991; Kosmider et al. 1967); however, the lack of statistical analysis precludes interpretation of these studies. Alterations in heart rate have also been reported. A decrease in heart rate (10–27% of controls) was observed in rats exposed to 75 ppm for 60 minutes (Kohno et al. 1991). In contrast, another study found an increase in heart rates in rats exposed to 100–200 ppm for 1 hour (Higuchi an Fukamachi 1977). The differences may be reflective of the different exposure levels. Data on the cardiotoxicity of hydrogen sulfide following longer-term exposure is limited to a study by CIIT (1983a, 1983b, 1983c). This study found no treatment-related histopathological alterations in the cardiovascular system of F-344 or Sprague-Dawley rats or $B6C3F_1$ mice exposed via inhalation to time-weighted-average (TWA) concentrations of 10, 30, or 80 ppm hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c).

Gastrointestinal Effects. Nausea and vomiting have been noted in several cases of human inhalational hydrogen sulfide poisoning (Allyn 1931; Audeau et al. 1985; Deng and Chang 1987; Krekel 1964; Osbern and Crapo 1981; Thoman 1969).

In two evaluations of the acute health effects associated with communities experiencing episodes of high emissions, significant increases in the reporting of nausea as a symptom have been reported (Haahtela et al. 1992; Marttila et al. 1995). In the first study, increased emissions from a pulp mill resulted in increased concentrations of hydrogen sulfide over 2 days. The highest 4-hour concentration of hydrogen sulfide was 135 $\mu g/m^3$ (96.4 ppb) and the 24-hour averages for the 2 days were 35 and 43 $\mu g/m^3$ (25 and 31 ppb). Following the high exposure, and then after a low exposure period (hydrogen sulfide level of 0.1 to 3.5 $\mu g/m^3$ [0.07–2.5 ppb] for 4 hours), community responses were evaluated with a questionnaire. In this comparison, the concentration of sulfur dioxide was the same. In a study, Marttila et al. (1995) compared community responses using six consecutive questionnaires after three predefined levels of exposure. The three exposure levels were expressed as $\mu g/m^3$ of TRS as a way to summarize the complex pollution mixture of hydrogen sulfide, methyl mercaptan, and methylsulfides produced by pulp mills using the sulfate pulping method. The three categories of exposure were low (daily mean of TRS <10 $\mu g/m^3$), (medium 10–30 $\mu g/m^3$), and high exposure (>30 $\mu g/m^3$). An increase in reports of nausea was significant only with the highest level of exposure. Interpretation of these results is complicated by the presence of multiple sulfur compounds as well as other air pollutants. Earlier work indicated that

hydrogen sulfide represented two-thirds of the TRS (Marttila et al. 1994a). Concurrent measurements of sulfur dioxide, total suspended particles, and nitrogen oxides for the periods covered by each of the questionnaires, indicated that only sulfur dioxide appeared to co-vary with TRS.

No treatment-related histopathological changes were detected in the gastrointestinal tract of F-344 or Sprague-Dawley rats or B6C3F_1 mice exposed via inhalation TWA concentrations of 10, 30, or 80 ppm hydrogen sulfide 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c). No gastrointestinal effects were reported in crossbred pigs exposed to 8.5 ppm hydrogen sulfide for 24 hours/day for 17 days (Curtis et al. 1975).

Hematological Effects. The cyanosis that has been reported in a number of cases of accidental exposure to hydrogen sulfide is believed to result from respiratory distress (Arnold et al. 1985; Burnett et al. 1977; Deng and Chang 1987; Peters 1981; Ravizza et al. 1982; Stine et al. 1976; Tvedt et al. 1991a, 1991b).

Complete blood counts were normal in four individuals overcome by unknown concentrations of hydrogen sulfide gas in a pelt room (Audeau et al. 1985). Percent hemoglobin saturation was unchanged by inhalation of either 5 ppm hydrogen sulfide by volunteers during 30-minutes of submaximal exercise (Bhambhani et al. 1994), or 10 ppm hydrogen sulfide during two 30-minute sessions of submaximal exercise (Bhambhani et al. 1997).

Workers who were sometimes exposed to airborne concentrations of >20 ppm hydrogen sulfide did not have any changes in hematological parameters (Ahlborg 1951). Pulp industry workers (n=17) exposed to 8-hour TWA concentrations of 0.05–5.2 ppm hydrogen sulfide had no signs of clinical anemia (Tenhunen et al. 1983). Jappinen and Tenhunen (1990) examined blood sulfide concentration and changes in heme metabolism at 2 hours, 1 week, and 1 month post-hydrogen sulfide poisoning in six cases of occupational exposure. Decreased delta-aminolaevulinic acid synthase activities and erythrocyte protoporphyrin concentrations were noted at the 2-hour and 1-week time periods, but not to the level of significance, and there was no change in heme synthase activity.

No treatment-related changes in hematological parameters were noted in F-344 or Sprague-Dawley rats or B6C3F_1 mice exposed by inhalation to TWA concentrations of 10, 30, or 80 ppm of hydrogen sulfide 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c).

Musculoskeletal Effects. In a series of reports characterizing the responses of healthy volunteers to low level, short-term exposures to hydrogen sulfide, Bhambhani and his colleagues (Bhambhani and Singh 1991; Bhambhani et al. 1994, 1996a, 1996b, 1997) concluded that exposures to 5 or 10 ppm hydrogen sulfide via oral inhalation resulted in increases in blood lactate concentrations and a decrease in muscle citrate synthase activity indicative of an inhibition of the aerobic capacity of exercising muscle. Men appeared to be more sensitive to this effect, showing a small response at 5 ppm where women did not show an effect until the 10 ppm level (Bhambhani et al. 1996b, 1997).

No treatment-related histopathological changes were detected in the skeletal muscle, bone marrow, or bone of F-344 or Sprague-Dawley rats or B6C3F_1 mice exposed to TWA concentrations of 10, 30, or 80 ppm hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days (1983a, 1983b, 1983c).

Hepatic Effects. Increases in unspecified liver enzyme activities were noted in some of 221 persons exposed by inhalation to hydrogen sulfide (Burnett et al. 1977). No baseline for these effects was available and they were not quantified.

No changes in serum protein, lactate dehydrogenase (LDH), serum glutamic-oxaloacetic transaminase (SGOT; AST), or alkaline phosphatase activities were noted in Sprague-Dawley rat dams exposed to 20, 50, or 75 ppm of hydrogen sulfide for 7 hours/day from gestation day 1 through postnatal day 21 (Hayden et al. 1990a). Maternal liver cholesterol levels were increased in Sprague-Dawley dams exposed to 75 ppm, but not 50 ppm, for 7 hours/day from gestation day 6 to postpartum day 21 (Hayden et al. 1990b).

No treatment-related histopathological changes were detected in the livers of F-344 or Sprague-Dawley rats or B6C3F_1 mice exposed to TWA concentrations of 10, 30, or 80 ppm of hydrogen sulfide 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c). No gross or histopathological lesions were found in the livers of crossbred pigs exposed to 8.5 ppm of hydrogen sulfide continuously for 17 days (Curtis et al. 1975).

Renal Effects. Blood urea nitrogen and serum electrolyte levels were normal in several individuals overcome by unknown concentrations of hydrogen sulfide gas in a pelt room (Audeau et al. 1985). One of these four patients had protein and blood in the urine initially, which was not detected upon later testing. Albumin and some granular casts were noted in the urine in another patient, but these findings were transient (Audeau et al. 1985).

F-344 and Sprague-Dawley rats as well as $B6C3F_1$ mice were exposed to TWA concentrations of 10, 30, or 80 ppm of hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c). No treatment-related histopathological changes were detected in the kidneys of these animals and urinalysis findings were negative, indicating no renal effects due to hydrogen sulfide exposure. No gross or histopathological lesions were found in the kidneys of crossbred pigs exposed to 8.5 ppm of hydrogen sulfide continuously for 17 days (Curtis et al. 1975).

Endocrine Effects. No studies were located regarding endocrine effects in humans after inhalation exposure to hydrogen sulfide.

No treatment-related histopathological changes were detected in the pituitary, adrenal, thyroid, or parathyroid glands of F-344 or Sprague-Dawley rats or $B6C3F_1$ mice exposed to TWA concentrations of 10, 30, or 80 ppm hydrogen sulfide 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c).

Dermal Effects. Six men lost consciousness after acute hydrogen sulfide exposure; one man with probable exposure to 8–16 ppm had peeling facial skin (Tvedt et al. 1991a, 1991b).

No treatment-related histopathological changes were detected in the skin of F-344 or Sprague-Dawley rats or $B6C3F_1$ mice exposed to TWA concentrations of 10, 30, or 80 ppm hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c). Slate-grey skin discoloration and erythema were noted in rabbits exposed to unspecified concentrations of hydrogen sulfide for 2 hours (Laug and Draize 1942).

Ocular Effects. Ocular effects reported after inhalation exposure are believed to have resulted from direct eye contact with hydrogen sulfide gas. Hydrogen sulfide gas is an eye irritant. Keratoconjunctivitis (sometimes with subsequent infection), punctate corneal erosion, blepharospasm, lacrimation, and photophobia have developed in individuals exposed to brief high-level concentrations of hydrogen sulfide gas (Ahlborg 1951; Luck and Kaye 1989). Hemorrhagic keratoconjunctivitis and subconjunctival hemorrhage were reported in cases of near-lethal poisoning to unknown concentrations of hydrogen sulfide (Deng and Chang 1987; Stine et al. 1976). A retrospective study of 250 Canadian workers who submitted workers' compensation claims for hydrogen sulfide exposure found that 18% had developed conjunctivitis, which persisted for several days in some cases (Arnold et al. 1985). Stinging of the eyes has been reported in acute occupational hydrogen sulfide poisoning (Audeau et al. 1985). None of these

reports of ocular exposure suggested that permanent eye effects may occur (Ahlborg 1951; Arnold et al. 1985; Audeau et al. 1985; Deng and Chang 1987; Luck and Kaye 1989; Stine et al. 1976). People exposed to hydrogen sulfide, methyl mercaptan, and methyl sulfides while living in a community around a paper mill reported eye irritation 12 times more often than people without exposure (Jaakkola et al. 1990). These effects were observed at mean annual hydrogen sulfide exposures estimated at 6 μg/m^3 (4.3 ppb). However, the ocular symptoms that were reported may have been due to exposure to peak concentrations of hydrogen sulfide (daily peaks as high as 100 μg/m^3; 70 ppb) and not annual mean concentrations, or may have been due to co-exposure to methyl mercaptan and methyl sulfides. Methyl mercaptan is also an eye irritant (NIOSH 1997) and it was also present at an annual mean concentration of 2–5 μg/m^3 with the highest daily average concentration being 50 μg/m^3 (Jaakkola et al. 1990).

In a retrospective epidemiologic study using hospital discharge data from 1981 to 1990, Bates et al. (1998) evaluated the risk of disease to known target organ systems of hydrogen sulfide toxicity in residents of Rotorua, a New Zealand city that uses geothermal energy for industrial and domestic heating purposes. No information on hydrogen sulfide levels was presented in this report, but the authors indicate concerns that exposures to hydrogen sulfide and/or mercury from geothermal sources could have health impacts. In their previous work, it was indicated that the most reliable monitoring information for hydrogen sulfide in the area came from a monitoring exercise in 1978, which found a median concentration of hydrogen sulfide of 20 μg/m^3, with 35% of the measurements >70 μg/m^3 and 10% >400 μg/m^3 (Bates et al. 1997). On the basis of hospital discharge data, significant increases in incidence were found for diseases of the nervous system and sense organs (SIR=1.11; $p<0.001$) among Rotorua residents as compared to the rest of New Zealand. When incidence rates were examined for minor disease groupings within this group of nervous system and sense organ diseases, significantly increased risks were seen for other disorders of the eye and adnexa (SIR=1.12; $p<0.001$). At the level of individual diseases, statistically significant incidence ratios were found for cataract (SIR=1.26; $p<0.001$), disorders of the conjunctiva (SIR=2.09; $p<0.001$), and disorders of the orbit (SIR=1.69; $p=0.005$). The effect of hydrogen sulfide on the eye is of considerable importance because ocular effects occur at concentrations that provide no other observable systemic effect (NIOSH 1977a).

Ocular irritation has also been noted after animals were exposed to hydrogen sulfide. Epiphora was noted in F-344 rats exposed to 400 ppm, but not 200 ppm, of hydrogen sulfide for 4 hours (Lopez et al. 1988b). Eye irritation was noted in guinea pigs exposed to 20 ppm of hydrogen sulfide 1 hour/day for 20 days (Haider et al. 1980). No ocular lesions were found upon microscopic examination of the eyes of crossbred pigs exposed to 8.5 ppm of hydrogen sulfide 24 hours/day for 17 days (Curtis et al. 1975).

No treatment-related histopathological changes were detected in the eyes of F-344 or Sprague-Dawley rats or B6C3F$_1$ mice exposed to TWA concentrations of 10, 30, or 80 ppm of hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c).

Body Weight Effects. No studies were located regarding body weight effects in humans after inhalation exposure to hydrogen sulfide.

Pregnant Sprague-Dawley rats exposed to 100 or 150 ppm hydrogen sulfide on gestation days 6–20 showed decreased body weight gains that reached significance at the higher dose. Absolute weight gain (i.e., minus the gravid uterine weight) was significantly depressed at both of these doses. Exposure at 50 ppm hydrogen sulfide had no effect on body weight gain or on absolute weight gain (Saillenfait al. 1989). No effects on body weight were noted in Sprague-Dawley rats exposed to 50 ppm of hydrogen sulfide 5 days/week, for 25 weeks (Gagnaire et al. 1986). No treatment-related body weight changes were noted in F-344 rats exposed to TWA airborne concentrations of 10, 30, or 80 ppm of hydrogen sulfide 6 hours/day, 5 days/week, for 90 days (CIIT 1983b). However, when Sprague-Dawley rats were exposed on the same regimen, females at 80 ppm showed a significant (10%) decrease in body weight at the end of the study compared to controls, which was not evident at 30 ppm (CIIT 1983c). At 80 ppm, the body weight of males was significantly less (8%) than controls during weeks 1–3, but the final body weight differences were not significant (CIIT 1983c). Similarly, B6C3F$_1$ mice of both sexes exposed to TWA concentrations of 80 ppm hydrogen sulfide 6 hours/day, 5 days/week, for 90 days showed decreases in body weight of 7–14% compared to controls; these changes were not observed at 30 ppm (CIIT 1983a). No body weight changes were found in crossbred pigs exposed to 8.5 ppm hydrogen sulfide continuously for 17 days (Curtis et al. 1975).

Metabolic Effects. Severe metabolic acidosis developed in a worker exposed to hydrogen sulfide generated from a sodium sulfide waste solution dumped onto acid waste material (Stine et al. 1976). Blood lactate concentrations were significantly increased (65%) compared to controls during exercise in men exposed to 5 ppm hydrogen sulfide via oral inhalation for more than 16 minutes (Bhambhani and Singh 1991), but not at 2 ppm. Additional studies by the same group (Bhambhani et al. 1994, 1996b) exposed both men and women to 5 ppm hydrogen sulfide during 30 minutes of exercise and failed to observe significant increases in lactate concentrations, but did see a decrease in muscle citrate synthase in men, suggesting that aerobic metabolism was being compromised at this level of exposure.

In a subsequent study, Bhambhani et al. (1997) observed significant increases in blood lactate concentrations in male and female volunteers exposed to 10 ppm hydrogen sulfide, although there was not a significant change in the activities of muscle lactate dehydrogenase, citrate synthase, or cytochrome oxidase.

In Sprague-Dawley rat dams exposed to 20, 50, or 75 ppm of hydrogen sulfide for 7 hours/day from gestation day 1 through postnatal day 21, blood glucose levels were increased about 50% at all exposure concentrations (Hayden et al. 1990a).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans after inhalation exposure to hydrogen sulfide.

No treatment-related histopathological changes were found in the spleen or lymph nodes of F-344 or Sprague-Dawley rats or $B6C3F_1$ mice exposed to TWA concentrations of 10, 30, or 80 ppm of hydrogen sulfide 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c). Pulmonary alveolar macrophage function was studied using lavage fluid from F-344 rats exposed for 4 hours to 50, 200, or 400 ppm hydrogen sulfide (Khan et al. 1991). Although the number of pulmonary alveolar macrophage cells was not influenced by hydrogen sulfide exposure, the number of viable cells was significantly decreased at 400 ppm. When the pulmonary alveolar macrophage cells were treated with Zymosan to stimulate respiration rates, it was found that there was no stimulation of respiration in cells from animals exposed to 200 or 400 ppm; these rates were significantly different from controls and were approximately equal to basal cell levels (Khan et al. 1991).

The highest NOAEL values and all reliable LOAEL values for immunological effects in rats and mice exposed in acute- and intermediate-duration studies are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.4 Neurological Effects

Acute human exposure to hydrogen sulfide can result in nausea, headaches, delirium, disturbed equilibrium, poor memory, neurobehavioral changes, olfactory paralysis, loss of consciousness, tremors,

and convulsions. Fatigue, poor memory, dizziness, and irritability have been observed in workers chronically exposed to hydrogen sulfide (Beauchamp et al. 1984).

Available information on the neurotoxic effects of acute exposures to high levels of hydrogen sulfide in humans comes primarily from case reports. In most instances, exposure concentrations were either unknown or estimated. In most cases, the exact exposure duration was not known, but estimated durations ranged from several minutes to an hour. The most commonly reported nonlethal effect found in individuals exposed to high concentrations is unconsciousness followed by apparent recovery, colloquially referred to as knockdown (Deng and Chang 1987; Krekel 1964; McDonald and McIntosh 1951; Milby 1962; Spolyar 1951). Other described neurological effects in the case reports include disturbed equilibrium, nausea, headache, poor memory, insomnia, irritability, delirium, severe vertigo, unusual sweating, neuropsychological symptoms, convulsions, and tremors (Arnold et al. 1985; Krekel 1964). While deaths were often noted, there were cases in which individuals survived and had complete neurological recovery (Deng and Chang 1987; Krekel 1964; Osbern and Crapo 1981; Ravizza et al. 1982). In a study of the possible effects of exposure to low concentrations of hydrogen sulfide, 3/10 asthmatic volunteers complained of headache after being exposed in a sealed chamber to 2 ppm hydrogen sulfide for 30 minutes (Jappinen et al. 1990).

A few case reports have described permanent or persistent neurological effects in humans following acute inhalation exposure to high concentrations of hydrogen sulfide. One patient developed symptoms of frontal headaches, irritability, poor concentration ability and attention span, and deficits of cortical function tests, including verbal abstraction, attention, and short-term retention 1 month after accidental exposure to unspecified concentrations of hydrogen sulfide (Stine et al. 1976). All effects except headaches resolved by 2 months after the accident. A 5–10-year follow-up re-examination of several individuals who became unconscious after exposure to unspecified concentrations of hydrogen sulfide revealed permanent neurological symptoms (Tvedt et al. 1991a, 1991b) including vision and memory impairment; rigid movements; reduced motor function; slight tremor; ataxia; psychosis; abnormal learning, retention, and motor function; and slight cerebral atrophy. The probable exposure concentration in one of the patients may have exceeded 200 ppm (as measured 2.5 hours after exposure). Divergent reports of the risk of permanent neurological damage due to hydrogen sulfide may result from lack of follow-up after hospital discharge (Tvedt et al. 1991b). Permanent neurologic damage including effects on balance, vibration sense, and impaired verbal and visual recall were observed in one man exposed to a very high concentration (14,000 ppm) of hydrogen sulfide (Kilburn 1993). In another case report, a worker who suffered ‘knockdown’ and presented in a coma, remained in a coma through standard

treatment (i.e., sodium nitrite), underwent several treatments with hyperbaric oxygen, and became responsive to simple commands by day 5. However, at the time of discharge, an extensive head injury assessment found effects on speech, attention span, insight, and ability to communicate, as well as a marked impact on visual memory and the ability to acquire, retain, and recall new information. These effects had not resolved by 12 and 18 months after exposure (Snyder et al. 1995). In a somewhat similar scenario, Schneider et al. (1998) describe a case in which another worker lost consciousness when he descended into a 27-foot pit that was part of a sewer construction project. He was overcome by hydrogen sulfide fumes (concentration not specified), fell from a ladder from an unspecified height, and was subsequently removed in a coma and transported to a local trauma center. At the emergency room (and potentially at the site), the patient experienced seizure activity. A body computed tomography (CT) scan showed pulmonary edema while a head CT scan was normal. The patient was transferred to a hyperbaric medicine unit and started on hyperbaric oxygen treatments (starting approximately 10 hours post-episode). Five days later, he recovered consciousness, and by 7 days, his status had improved enough to discontinue hyperbaric oxygen treatments. He was able to feed himself and move with assistance, but had impaired language, memory, and attention, and appeared agitated and restless. Over the course of the next 4 years, the patient was evaluated on a variety of occasions. He continued to show a constellation of deficits, which even 4 years later, included problems with general cognition, motor function, and cognitive function; some of these symptoms appeared to be alleviated through a combined treatment with fairly high doses of Ritalin and Cyclert drugs, which enhance dopaminergic functioning.

In a case control study of 16 subjects who had been exposed for minutes, hours, or years to hydrogen sulfide, Kilburn (1997) found evidence of permanent neurobehavior impairment in exposed individuals when compared to 353 controls matched for sex, age, and years of education. A large battery of tests was used to evaluate these individuals, including a detailed self-administered questionnaire, complete physical and clinical screen neurologic examinations, as well as a series of neurophysiologic and neuropsychologic tests. Among those who had chronic low-dose exposure, the most sensitive tests were those evaluating balance, simple reaction time, left visual field, and verbal recall. The group exposed to hydrogen sulfide for hours showed additional defects, including impacts on a variety of neuropsychological tests, although remote memory remained intact. The group that experienced momentary knock-down exposure had an even larger suite of deficit cognitive functions, leading the study author to conclude that "...brief high doses were devastating, whereas protracted low doses showed effects on the more sensitive tests."

A 20-month-old child was exposed for nearly 1 year to >0.6 ppm hydrogen sulfide and other emitted chemicals from a coal mine (Gaitonde et al. 1987). Symptoms included ataxia, choreoathetosis, dystonia,

and inability to stand. A CT scan of the brain showed bilateral areas of low density in the region of both basal ganglia and surrounding white matter. Neurophysiological investigations of electroencephalography, visual evoked responses, brain stem evoked responses, and peripheral nerve conduction studies were normal. The child's condition improved spontaneously, shortly after hospital admission; after 10 weeks, ataxia had resolved and the choreoathetoid movements were reduced. A repeat brain scan showed complete resolution of abnormalities. The relationship of these complaints to low-level hydrogen sulfide exposure is unclear.

Neurological effects resulting from chronic-duration exposure to hydrogen sulfide in the shale industry have been reported (Ahlborg 1951). Symptoms observed in workers exposed to daily concentrations of hydrogen sulfide that often exceeded 20 ppm included fatigue, loss of appetite, headache, irritability, poor memory, and dizziness. The frequency of fatigue increased with length of employment and the degree of hydrogen sulfide exposure.

In the South Karelia air pollution study, discussed in more detail under respiratory effects, all of the reports found increases in the incidence of headaches or migraines in polluted communities when compared to nonpolluted communities (Jaakkola et al. 1990; Marttila et al. 1994b, 1995; Partti-Pellinen et al. 1996); however, only in the most recent study did this finding achieve statistical significance. Using a cross-sectional, self-administered questionnaire, this report (Partti-Pellinen et al. 1996) evaluated the increased risk of headache or migraine in adults in a slightly polluted and a reference community. In the polluted community, the mean annual TRS concentrations were 2–3 $\mu g/m^3$, the 24-hour concentrations varied between 0 and 56 $\mu g/m^3$, and the maximum 1-hour concentration was 155 $\mu g/m^3$; there was no TRS detected in the reference community. In the polluted community, the sulfur dioxide annual mean concentration was 1 $\mu g/m^3$, the 24-hour concentrations varied between 0 and 24 $\mu g/m^3$ and the maximum 1-hour concentration was 152 $\mu g/m^3$. In the reference community, the mean sulfur dioxide level was 1 $\mu g/m^3$ and the maximum 1-hour concentration was 30 $\mu g/m^3$. The residents of the polluted community showed a significantly increased risk of headache both during the previous 4-week period (OR=1.83; 95% CI=1.06–3.15) and the preceding 12 months (OR=1.70; 95% CI=1.01–2.64), when compared to the residents of the reference community, even after adjusting for differences in age, gender, smoking, history of allergic diseases, education, and marital status between the two communities.

In a retrospective epidemiologic study using hospital discharge data from 1981 to 1990, Bates et al. (1998) evaluated the risk of disease to known target organ systems of hydrogen sulfide toxicity in residents of Rotorua, a New Zealand city that uses geothermal energy for industrial and domestic heating

purposes. Although no information on hydrogen sulfide levels was presented in this report, the authors' previous work indicated that a monitoring exercise in Rotorua in 1978 found a median concentration of hydrogen sulfide of 20 μg/m^3, with 35% of the measurements >70 μg/m^3 and 10% >400 μg/m^3; additionally, elevated concentrations of mercury had previously been found in the hair of residents (Bates et al. 1997). Significant increases in incidence were found for diseases of the nervous system and sense organs (SIR=1.11; $p<0.001$) among Rotorua residents as compared to the rest of New Zealand residents. When the data were stratified by gender and ethnicity, the increased risks remained significant for all but non-Maori men. When incidence rates were examined for minor disease groupings within nervous system diseases, significantly increased risks were seen for other disorders of the central nervous system (SIR=1.22; $p<0.001$) and disorders of the peripheral nervous system (SIR=1.35; $p<0.001$). At the level of individual diseases, statistically significant incidence ratios were found for infant cerebral palsy (SIR=1.42; $p=0.02$), migraine (SIR=1.40; $p=0.002$), other conditions of the brain (SIR=2.50; $p<0.001$), mononeuritis of the upper limbs and mononeuritis multiplex (SIR=1.47; $p<0.001$), and mononeuritis of the lower limbs (SIR=2.06; $p<0.001$). A follow-up study of this population found a significant exposure-related trend ($p<0.001$) for increasing incidence of diseases of the nervous system and sense organs (Bates et al. 2002). In this study, the hospital discharge records were used to obtain disease incidence data; additionally, the affected individuals were divided into three exposure groups (low, medium, and high) based on their current residence. Actual exposure levels were not monitored; a surrogate for exposure was used. When the nervous system disease incidence was further divided into subcategories, significant trends ($p<0.001$) were found for other disorders of the central nervous system, disorders of the eye and adnexa, and disorders of the ear and mastoid process. The SIRs (95% confidence interval) were significantly elevated in all groups for disorders of the eye and adnexa: 1.47 (1.33–1.63), 1.57 (1.30–1.89), and 2.27 (1.97–2.61) for the low, medium, and high exposure groups, respectively. In the high exposure group, the SIRs were also elevated for other disorders of the central nervous system (2.59, 1.91–3.44), disorders of the peripheral nervous system (2.27, 1.97–2.61), and disorders of the ear and mastoid process (2.00, 1.65–2.40). The lack of exposure data, the assumption that hydrogen sulfide exposure only occurred at home, the assumption that current exposure also represented historical exposure, and the lack of control for confounding variables such as smoking and socioeconomic status limit the interpretation of these data.

ATSDR (Inserra et al. 2004) examined residents of Dakota City, Nebraska for neurobehavioral effects resulting from chronic exposure to ≥90 ppb hydrogen sulfide. Although the 90 ppb level was used as a cut off value, historical monitoring data records showed much higher levels; for example, the outdoor hydrogen sulfide level exceeded 1,000 ppb 275 times in the 1995–1999 time period. Hydrogen sulfide

exposure did not appear to adversely affect performance on most neurobehavioral tests; in fact, the hydrogen sulfide exposed groups scored better than the referent group on 21 of the 28 tests, although the differences were not statistically significant. The hydrogen sulfide group did score lower on a memory test (match to sample score) and a test of grip strength, but the differences were not statistically significant.

Rabbits exposed to 72 ppm of hydrogen sulfide for 1.5 hours lost consciousness (Kosmider et al. 1967). Haider et al. (1980) observed behaviors in guinea pigs exposed daily to 20 ppm of hydrogen sulfide for 11 days that were indicative of fatigue, somnolence, and dizziness; no additional information of overt behaviors were provided. Neurochemical analyses revealed decreased cerebral hemisphere and brain stem total lipids and phospholipids. Rats exposed to 800 ppm of hydrogen sulfide for 20 minutes lost consciousness (Beck et al. 1979). Lethargy was observed in rats following exposure to 400 ppm of hydrogen sulfide for 4 hours (Lopez et al. 1988b).

Male Wistar rats were exposed to average concentrations of 100–200, 200–300, 300–400, or 400–500 ppm hydrogen sulfide; at 200–300 ppm, a decreased response rate in a discriminated avoidance task was observed (Higuchi and Fukamachi 1977). Except at the highest concentrations tested, the response rates and percent avoidances recovered rapidly when ventilation with clean air was provided, although even at 400–500 ppm, they were almost normal the following day (Higuchi and Fukamachi 1977). When these same animals were tested for Sidman-type conditioned avoidance response at response-shock intervals of 10 or 30 seconds, an inverse relationship between hydrogen sulfide concentration and response rate was noted (Higuchi and Fukamachi 1977); this effect dissipated when exposure stopped.

Female NMRI mice were exposed to 100 ppm of hydrogen sulfide for 2 hours at 4-day intervals; excitement was observed (Savolainen et al. 1980). Exposure also resulted in decreased cerebral ribonucleic acid (RNA), decreased orotic acid incorporation into the RNA fraction, and inhibition of cytochrome oxidase. An increase in the glial enzyme marker, 2’,3’-cyclic nucleotide-3’-phospho-hydrolase, was seen. Neurochemical effects have been reported in other studies. Decreased leucine uptake and acid proteinase activity in the brain were observed in mice exposed to 100 ppm hydrogen sulfide for 2 hours (Elovaara et al. 1978). Inhibition of brain cytochrome oxidase and a decrease in orotic acid uptake were observed in mice exposed to 100 ppm hydrogen sulfide for up to 4 days (Savolainen et al. 1980).

Significant decreases in motor activity (ambulations and total movements) were observed in rats receiving nose-only exposure to 80, 200, or 400 ppm hydrogen sulfide 3 hours/day for 5 days (Struve et al. 2001). However, a decrease in motor activity was not observed in rats receiving whole-body exposures to 80 ppm 3 hours/day for 5 days (Struve et al. 2001). The study authors did not discuss these conflicting results. In addition, significant impairment of learning and memory, as assessed in a water maze test, was observed in rats receiving nose-only exposure to 400 ppm. However, these results should be interpreted cautiously because the impaired learning and memory may have been secondary to the decrease in motor activity and decreased body temperature also observed in these animals.

A series of intermediate-duration studies conducted by Partlo et al. (2001) used the radial arm maze to assess the effect of hydrogen sulfide on learning and memory in rats exposed to 125 ppm hydrogen sulfide 4 hours/day, 5 days/week for 5–11 weeks. In the first study, the rats were trained on the radial arm maze prior to hydrogen sulfide exposure; 5 weeks of hydrogen sulfide exposure did not adversely affect post-exposure performance on the maze, suggesting that 5 weeks of exposure to hydrogen sulfide did not adversely affect memory. In the second study, the rats were exposed to hydrogen sulfide and trained on the maze daily for 11 weeks. The results of this study suggest that hydrogen sulfide did not interfere with acquisition of the maze task, but did adversely affect performance rate. In the third study, the rats from the second study were retrained on a modified radial arm maze without additional exposure to hydrogen sulfide. These results suggested that the hydrogen sulfide-exposed rats had difficulty re-learning a complex task.

The intermediate-duration effects of hydrogen sulfide on neurological function were examined by the measurement of motor and sensory nerve conduction velocities of the tail nerve or morphology of the sciatic nerve (Gagnaire et al. 1986). Male Sprague-Dawley rats were exposed to 0 or 50 ppm hydrogen sulfide for 5 days/week, for 25 weeks. The study authors did not report the duration of exposure to hydrogen sulfide per day. No neurotoxic effects were observed in the rats.

Neurologic function and neuropathology were evaluated in Sprague-Dawley rats exposed to 0, 10, 30, or 80.0 ppm hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days (CIIT 1983c). Neurological function evaluation included: an assessment of posture; gait; tone of facial muscles; pupillary, palpebral, extensor thrust; and crossed-extensor thrust reflexes. Besides routine neuropathologic examinations, special studies included an examination of teased fibers from muscular and sural branches of the tibial nerve together with specimens from cervical and lumbar spinal cord. Absolute brain weights were

decreased (5%) in male rats exposed to 80 ppm hydrogen sulfide in this study; however, there were no treatment-related effects on neurological function or neuropathology.

No signs of neurotoxicity were noted in a similar study in which F-344 rats were exposed to 0, 10, 30, or 80 ppm hydrogen sulfide for 90 days (CIIT 1983b). Likewise, no treatment-related neurological effects were observed in male and female $B6C3F_1$ mice exposed to 0, 10.1, 30.5, or 80.0 ppm hydrogen sulfide for 90 days (CIIT 1983a).

The highest NOAEL values and all reliable LOAEL values for neurological effects in rats, guinea pigs, mice, and rabbits from acute- or intermediate-duration studies are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.5 Reproductive Effects

There are limited data on the reproductive toxicity of hydrogen sulfide in humans. Hemminki and Niemi (1982) examined the spontaneous abortion rate in relationship to maternal and paternal occupation and residential environmental pollution in an industrial community in Finland. Women who were employed in rayon textile and paper products jobs had an increased rate of spontaneous abortions ($p<0.10$), as did women whose husbands worked in rayon textile or chemical processing jobs. This study also examined the possible relationship between exposure to sulfur dioxide, hydrogen sulfide, and carbon disulfide and the occurrence of spontaneous abortions. A non-statistically significant increase in the incidence of spontaneous abortion was observed in women living in areas with hydrogen sulfide concentrations exceeding 2.85 ppm. Interpretation of these results are limited by the lack of control of other potential confounding variables, particularly occupational exposure to other chemicals. In a retrospective study of spontaneous abortions in a large population of women working in the petrochemical industry in China, Xu et al. (1998) reported a significantly increased risk of spontaneous abortion with frequent exposure to petrochemicals (OR of 2.7; 95% CI=1.8–3.9). When the risk associated with exposure to specific chemicals was examined, exposure to hydrogen sulfide was found to have an OR of 2.3 (95% CI=1.2–4.4).

No treatment-related histopathological changes were found in male or female reproductive organs of F-344 or Sprague-Dawley rats or $B6C3F_1$ mice exposed to TWA concentrations of 10, 30, or 80 ppm hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c). No significant alterations in gestation length, viability, or litter size were observed in Sprague-Dawley rats exposed to 0,

20, 50, or 75 ppm hydrogen sulfide for 7 hours/day on gestation days 6–21 (Hayden et al. 1990b). An apparent increase in parturition time was observed in the hydrogen sulfide-exposed dams; the mean lengths of parturition were 105.0, 148.8, and 117.5 minutes, compared to 85.2, 124, and 82.5 minutes in the three control groups; these data were not statistically analyzed. The study authors noted that increased parturition time was observed in 6 out of 18 exposed animals and in 1 of 17 controls. Dorman et al. (2000) did not find any significant alterations in gestation length in Sprague-Dawley rats exposed to 10, 30, or 80 ppm hydrogen sulfide for 6 hours/day, 7 days/week for 2 weeks prior to mating with exposed males, during the 2 week mating period, and on gestational days 0–19. This study also found no significant alterations in fertility (as assessed by mating index, fertility index, postimplantation loss, late resorptions, or still births), number of females with live pups, litter size, or number of implants per female. No histological alterations in the reproductive organs and accessory sex organs of rats in the controls and 80 ppm group were found; a slight, nonstatistically significant increase in the incidence of testicular degeneration was observed at 80 ppm. Additionally, no significant alterations in sperm count or morphology were observed.

The highest NOAEL values for reproductive effects in rats and mice from intermediate-duration studies are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to hydrogen sulfide.

No changes in serum protein, LDH, SGOT, or alkaline phosphatase activities were noted in the offspring of Sprague-Dawley rats exposed to 20, 50, or 75 ppm hydrogen sulfide for 7 hours/day from gestation day 1 through postnatal day 21 (Hayden et al. 1990a). No effects on blood glucose were noted in the offspring, although glucose levels were increased by about 50% in dams at all exposure concentrations on postnatal day 21 (Hayden et al. 1990a). In a second study, these authors (Hayden et al. 1990b) found a dose-related increase in parturition time in animals exposed to 20, 50, or 75 ppm hydrogen sulfide for 7 hours/day from gestation day 6 until postpartum day 21. The study also showed developmental delays in pinna attachment and hair growth, but these effects were not dose related.

No fetal effects were noted in a dose range-finding developmental study in which pregnant Sprague-Dawley rats were exposed to 150 ppm hydrogen sulfide on gestation days 6–20, despite body weight loss in the dams (Saillenfait et al. 1989).

No significant alterations in the incidence of structural anomalies were found in the offspring of Sprague-Dawley rats exposed to 10, 30, or 80 ppm hydrogen sulfide 6 hours/day, 7 days/week on gestational days 0–19 (Dorman et al. 2000). Continued exposure on postnatal days 5–18 did not result in developmental delays (pinnae detachment, surface righting, incisor eruption, negative geotaxis, and eyelid detachment), performance on developmental neurobehavioral tests (motor activity, passive avoidance, acoustic startle, or functional observation battery), or brain histopathology.

An examination of Purkinje cells from Sprague-Dawley rat pups exposed to 20 or 50 ppm hydrogen sulfide for 7 hours/day from gestation day 5 through postpartum day 21 showed severe alterations in the architecture and growth characteristic of the Purkinje cell dendritic fields compared to controls (Hannah and Roth 1991). The study did not mention whether any maternal effects were observed; however, the authors did indicate that "these findings suggest that developing neurons exposed to low concentrations of hydrogen sulfide are at risk of severe deficits." Two studies by Hannah et al. (1989, 1990) examined the effects of prenatal exposure to hydrogen sulfide on amino acid levels in the brain. In the first study, pregnant Sprague-Dawley rats were exposed to 75 ppm hydrogen sulfide for 7 hours/day, from postcoitus day 5 to postpartum day 21 (Hannah et al. 1989). Aspartate, glutamate, and GABA in the cerebrum and cerebellum were significantly reduced (about 20%) compared to controls by postpartum day 21. Taurine levels of the offspring were initially 25% higher than controls but had returned to control range by postpartum day 21; taurine levels were not measured in dams. In the 1990 study, pregnant Sprague-Dawley rats were exposed to 50 ppm hydrogen sulfide for 7 hours/day, from postcoital day 6 to postpartum day 21 (Hannah et al. 1990). In this study, maternal taurine levels were determined on parturition and on postpartum day 21. Taurine in maternal plasma was 30% higher than controls; taurine levels were not determined in offspring, so relating these levels to high taurine levels found in offspring in the 1989 study is speculative.

Further investigation into the developmental neurological effects of hydrogen sulfide was undertaken by Skrajny et al. (1992). Pregnant Sprague-Dawley rats were exposed to 20 or 75 ppm hydrogen sulfide 7 hours/day from gestation day 5 to postpartum day 21; separate control groups were used for each exposure level. Exposure to 20 ppm caused significant increases compared to controls in serotonin levels in the frontal cortex on postpartum day 21. Exposure to 75 ppm hydrogen sulfide caused significant

increases compared to controls in levels of serotonin in the cerebellum and cortex on postpartum days 14 and 21. Norepinephrine levels were significantly increased compared to controls at 75 ppm in the cerebellum and the frontal cortex. At 20 ppm, norepinephrine levels were below control levels by days 14 and 21, and in the cerebellum, levels fluctuated but were normal by postpartum day 21 (Skrajny et al. 1992). In a subsequent study using the same exposure regimen (i.e., between day 5 postcoital until day 21 postnatal), but following the monoamine levels in various regions of the brain up to 60 days postnatal, Roth et al. 1995 found that the alterations of monoamine levels observed at day 21 postnatal (the last day of exposure) gradually returned to control values by day 45.

The highest NOAEL and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.7 Cancer

There was no increase in cancer incidence noted in a residential cohort study of individuals living downwind from natural gas refineries in Alberta, Canada, from 1970 to 1984 (Schechter et al. 1989). In a retrospective epidemiologic study using cancer registry data from 1981 to 1990, Bates et al. (1998) evaluated the risk of cancer to known target organ systems of hydrogen sulfide toxicity in residents of Rotorua, a New Zealand city that uses geothermal energy for industrial and domestic heating purposes. No information on hydrogen sulfide levels was presented in this report, but the authors indicate concerns that exposures to hydrogen sulfide and/or mercury from geothermal sources could have health impacts. In their previous work, it was indicated that the most reliable monitoring information for hydrogen sulfide in the area came from a monitoring exercise in 1978 that found a median concentration of hydrogen sulfide of 20 $\mu g/m^3$, with 35% of the measurements over 70 $\mu g/m^3$ and 10% over 400 $\mu g/m^3$ (Bates et al. 1997). Based on the cancer registry information, these workers found a significantly increased risk of nasal cancers (SIR=3.17; p=0.01) among Rotorua residents as compared to the rest of the population of New Zealand. However, since this is a rare cancer, this finding is based on only four cancers. Because the population of Rotorua has a higher percentage of Maoris than the rest of New Zealand, these researchers also examined their data stratified by ethnicity and sex and found a significantly increased risk of cancers of the trachea, bronchus, and lung (SIR=1.48; p=0.02) among female Maoris in Rotorua as compared to female Maoris in the rest of New Zealand. Differences in smoking history between these two populations were not sufficient to explain the observed differences in risk. The authors concluded that the lack of adequate exposure information did not permit findings of causal relationships between

hydrogen sulfide and cancer incidence. The potential co-exposure to mercury also confounds the interpretation of these results.

No studies were located regarding cancer effects in animals after inhalation exposure to hydrogen sulfide.

3.2.2 Oral Exposure

3.2.2.1 Death

No studies were located regarding death in humans or animals after oral exposure to hydrogen sulfide.

3.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, or metabolic effects after oral exposure to hydrogen sulfide.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to hydrogen sulfide.

Diarrheic digestive disorder was observed in adult pigs fed hydrogen sulfide at a dose level of 15 mg/kg/day for a few days (Wetterau et al. 1964). The study authors reported that in a repeat study using younger pigs that weighed less, no diarrheic disorder was noted.

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to hydrogen sulfide.

Decreased body weight gain (48.2 kg total weight gain in treated animals versus 62.5 kg total weight gain in controls) was observed in pigs fed hydrogen sulfide at a dose level of 6.7 mg/kg/day for 105 days (Wetterau et al. 1964).

No studies were located regarding the following health effects in humans or animals after oral exposure to hydrogen sulfide:

3.2.2.3 Immunological and Lymphoreticular Effects

3.2.2.4 Neurological Effects

3.2.2.5 Reproductive Effects

3.2.2.6 Developmental Effects

3.2.2.7 Cancer

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to hydrogen sulfide.

A study by Laug and Draize (1942) reported death in two out of three rabbits exposed to unknown concentrations of hydrogen sulfide through either clipped, intact, or abraded skin. One rabbit with intact skin exposed to hydrogen sulfide for 2 hours survived, while another died in this interval. The rabbit exposed to hydrogen sulfide through abraded skin also died (Laug and Draize 1942). When two guinea pigs were exposed to unknown concentrations of hydrogen sulfide gas for 60 minutes on a small area of their shaved abdomen, neither died (Walton and Witherspoon 1925). However, both guinea pigs that had their entire shaved torso (about 50% body area) exposed to an unknown concentration of hydrogen sulfide died after about 45 minutes (Walton and Witherspoon 1925). No clinical signs of toxicity were seen in a dog with shaved abdomen exposed full body (except head) to unknown concentrations of hydrogen sulfide in a chamber for 1 hour (Walton and Witherspoon 1925).

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, or body weight effects in humans or animals after dermal exposure to hydrogen sulfide. However, several sources indicate that care must be taken

with liquefied hydrogen sulfide in order to avoid frostbite (Agency for Toxic Substances and Disease Registry 1994; NIOSH 1997).

3.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans or animals after dermal exposure to hydrogen sulfide.

3.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans after dermal exposure to hydrogen sulfide.

No clinical signs of neurotoxicity were seen in two guinea pigs exposed to an unknown concentration of hydrogen sulfide gas for 60 minutes on a small area of their shaved abdomen (Walton and Witherspoon 1925). A dog exposed to an unknown concentration of hydrogen sulfide for 1 hour showed no clinical signs of neurotoxicity (Walton and Witherspoon 1925).

No studies were located regarding the following health effects in humans or animals after dermal exposure to hydrogen sulfide:

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.3 GENOTOXICITY

No studies were located regarding genotoxicity in humans after inhalation exposure to hydrogen sulfide. No mutagenicity was observed with hydrogen sulfide gas in Ames assays using *Salmonella typhimurium* TA97, TA98, and TA100 strains, either with or without S9 liver fractions, of male Syrian golden hamsters or Sprague-Dawley rats that had been induced with 500 mg/kg Aroclor 1254 (EPA 1984).

However, it should be noted that the concentration of hydrogen sulfide gas was limited by its solubility in ethanol, which was the test solvent (EPA 1984). The highest dose that could be obtained was 1,750 µg/plate.

3.4 TOXICOKINETICS

Although hydrogen sulfide is primarily absorbed through the lungs, it can also be absorbed through the gastrointestinal tract and intact skin (Laug and Draize 1942; Wetterau et al. 1964). It is metabolized through three pathways: oxidation, methylation, and reactions with metalloproteins or disulfide-containing proteins (Beauchamp et al. 1984). Although the major metabolic pathway for detoxification of hydrogen sulfide is oxidation in the liver, the methylation pathway also serves as a detoxification route (EPA 1987a; Weisiger and Jakoby 1980). The major oxidation product of sulfide is thiosulfate, which is then believed to be converted to sulfate and subsequently excreted in urine (Bartholomew et al. 1980). Hydrogen sulfide is widely distributed in the body. Sulfides have been found in the liver, blood, brain, lungs, spleen, and kidneys of humans who died after accidental inhalation exposure. Hydrogen sulfide is excreted primarily as sulfate (free sulfate or thiosulfate) in the urine. It is also excreted unchanged in exhaled air and in feces and flatus.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Hydrogen sulfide is absorbed rapidly through the lungs (Adelson and Sunshine 1966; Allyn 1931; Breysse 1961; Deng and Chang 1987; Hagley and South 1983; Kimura et al. 1994; NIOSH 1989; Osbern and Crapo 1981; Parra et al. 1991). Inhalation absorption of lethal concentrations of hydrogen sulfide is rapid in humans, and effects can occur within seconds to minutes. Inhalation is the most common route of hydrogen sulfide exposure. Hydrogen sulfide dissociates at physiological pH to the hydrogen sulfide anion, which is probably the absorbed form (WHO 1987). No quantitative data are available regarding the absorption of hydrogen sulfide in humans.

Animal data, while demonstrating that absorption of hydrogen sulfide via the lungs occurs readily and rapidly, are not sufficient to quantitatively determine the proportion of an inhaled dose that is absorbed (Beck et al. 1979; Kage et al. 1992; Khan et al. 1990; Lopez et al. 1989; Nagata et al. 1990; Prior et al.

1988, 1990; Smith and Gosselin 1964; Tansy et al. 1981). No physiologically based pharmacokinetic (PBPK) models have been developed to provide estimates of hydrogen sulfide absorption.

3.4.1.2 Oral Exposure

Hydrogen sulfide exists as a gas; therefore, oral exposure to hydrogen sulfide will not normally occur. No studies were located regarding absorption in humans after oral exposure to hydrogen sulfide. Some case reports showing accidental oral ingestion of liquid manure or other substances that might contain hydrogen sulfide exist, but in all of these cases, the ingestion was secondary to being "knocked down" by inhalation of hydrogen sulfide (Freireich 1946; Imamura et al. 1996; Kimura et al. 1994; Osbern and Crapo 1981).

One animal study suggests that hydrogen sulfide can be absorbed through the gastrointestinal tract. A study where pigs were fed diets containing dried greens with levels of hydrogen sulfide of 1.5, 3.1, or 6.7 mg/kg/day for 105 days indicated that hydrogen sulfide is absorbed following ingestion (Wetterau et al. 1964).

3.4.1.3 Dermal Exposure

No studies were located regarding absorption in humans after dermal hydrogen sulfide exposure.

Animal data have shown that dermal hydrogen sulfide absorption can occur, although large surface areas of skin must be exposed. Trunk fur of rabbits was clipped for exposure to unknown concentrations of hydrogen sulfide gas for 1.5–2 hours; evidence for the absorption of hydrogen sulfide included both the death of the animals and a positive sulfide reaction of expired air with lead acetate paper (Laug and Draize 1942). No evidence of dermal absorption was found in two guinea pigs exposed to unknown concentrations of hydrogen sulfide gas for 1 hour on a small area of their shaved abdomens (Walton and Witherspoon 1925). Dermal absorption was indicated, however, when the entire torso of guinea pigs was exposed to hydrogen sulfide gas and the animals died after about 45 minutes (Walton and Witherspoon 1925). No clinical signs of toxicity were reported in a dog that received full-body exposure (except head) to unknown concentrations of hydrogen sulfide (Walton and Witherspoon 1925).

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

Few human data are available regarding tissue distribution after inhalation exposure to hydrogen sulfide. One case study reported sulfide (as bis[pentafluourobenzyl]sulfide) distribution in three of four men who drowned after being overcome, presumably, by hydrogen sulfide and falling unconscious into a lake in Japan (Kimura et al. 1994). Concentrations of hydrogen sulfide gas were estimated to be 550–650 ppm, based upon extrapolation of tissue concentrations from rat studies (Kimura et al. 1994; Nagata et al. 1990). Initial blood sulfide concentrations determined 2–3 hours postmortem in these individuals were 0.1, 0.2, and 0.08 µg/g tissue, while at 24 hours after death, the levels were 0.5 µg/g, 0.23 µg/g, and undetected, respectively. At 24 hours after death, sulfide concentrations in the brains of these individuals were 0.2, 0.4, and 1.06 µg/g, and lung concentrations were 0.68, 0.21, and 0.23 µg/g. Based on a study in rats by this same group of researchers (Nagata et al. 1990) that showed little or no increase in sulfide concentrations in rat lung and brain 24 hours after death, as well as a lack of sulfide in these tissues in control rats, Kimura et al. postulated that the sulfide levels observed in the brain and lungs in the human study may be indicators of tissue levels at the time of death (Kimura et al. 1994). Sulfide was detected in liver (1.30–1.56 µg/g), spleen (0.32–0.64 µg/g), and kidney (0.47–1.50 µg/g) (Kimura et al. 1994). Hydrogen sulfide levels of 0.92 µg/g in blood, 1.06 µg/g in brain, 0.34 µg/g in kidney, and 0.38 µg/g in liver were detected at autopsy in a man who was overcome by hydrogen sulfide in a tank (Winek et al. 1968). Hydrogen sulfide concentrations in the tank after the accident were 1,900–6,100 ppm (Winek et al. 1968).

Data from animal studies suggest that the distribution of inhaled hydrogen sulfide is rapid and widespread, while storage of hydrogen sulfide in the body is limited by rapid metabolism and excretion. Adult male rats exposed to 550 or 650 ppm hydrogen sulfide until death had tissue samples taken at 0, 4, 24, and 48 hours after death (Nagata et al. 1990). Sulfide concentrations were measured 1, 7, and 30 days later. Immediately after death, sulfide concentrations in whole blood were 0.48 µg/g in exposed animals and were nondetectable in control animals. Sulfide concentrations rapidly increased with time after death in both control and treated animals. Significant increases in sulfide concentrations were found in the lung (0.60 µg/g), brain (0.31 µg/g), thigh muscle (0.21 µg/g), and abdominal muscles (0.22 µg/g), as compared to controls (tissues collected immediately after death) (Nagata et al. 1990). Liver and kidney samples had similar sulfide concentrations in both exposed and control groups when taken immediately after death. Certain tissues (blood, liver, and kidneys) exhibited an increase in sulfide concentration with time after

death, whether hydrogen sulfide exposure occurred or not, while other tissues (lung, brain, and muscle) had little or no change in sulfide concentration (Nagata et al. 1990).

Distribution of hydrogen sulfide in male Wistar rats was examined by Kohno et al. (1991). Animals exposed to 75 ppm hydrogen sulfide for 20, 40, or 60 minutes showed essentially the same distribution of hydrogen sulfide irrespective of duration: 10 µg/mL blood, 25 µg/g brain, 20 µg/g lung, 37 µg/g heart, 20 µg/g liver, 25 µg/g spleen, and 30 µg/g kidney. The levels in the brain, lung, heart, liver, spleen, and kidney were significantly ($p>0.01$) higher than blood levels after 20 minutes of exposure.

Japanese white rabbits exposed to 500–1,000 ppm of hydrogen sulfide (the lethal concentration), for 60 minutes, had thiosulfate concentrations of 0.08 µmol/mL in blood, 0.095 µmol/g in lung, and 0.023 µmol/g in brain (Kage et al. 1992). Little or no thiosulfate was found in the liver, kidney, or muscle. When rabbits were exposed to 100–200 ppm of hydrogen sulfide for 60 minutes, blood thiosulfate levels decreased from 0.061 µmol/mL immediately postexposure to a trace level at 2 hours postexposure (Kage et al. 1992).

3.4.2.2 Oral Exposure

No studies were located regarding tissue distribution in humans or animals after oral exposure to hydrogen sulfide.

3.4.2.3 Dermal Exposure

No studies were located regarding tissue distribution in humans or animals after dermal exposure to hydrogen sulfide.

3.4.2.4 Other Routes of Exposure

No studies were located regarding tissue distribution in humans or animals after hydrogen sulfide exposure by other routes.

3.4.3 Metabolism

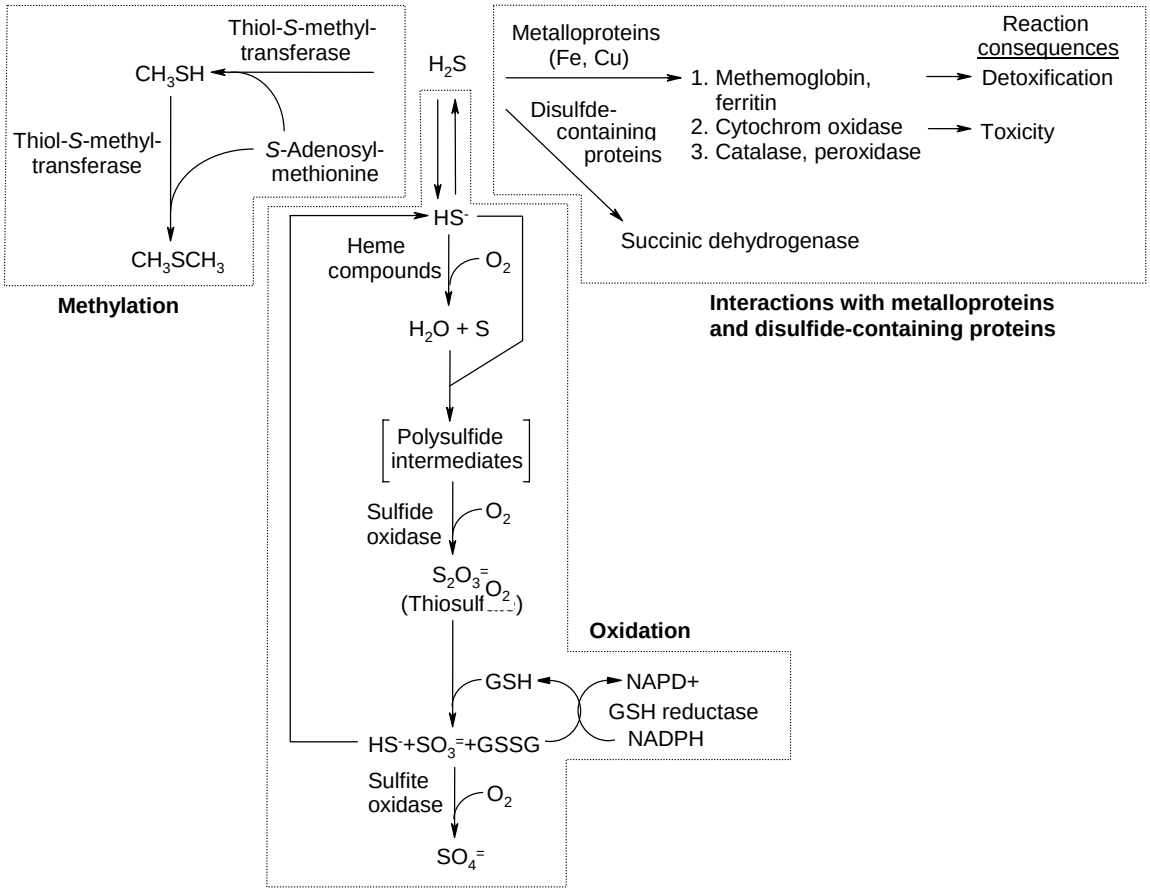
Hydrogen sulfide metabolism occurs through three pathways: oxidation, methylation, and reaction with metallo- or disulfide-containing protein (Beauchamp et al. 1984; EPA 1987a). Hydrogen sulfide is primarily detoxified by oxidation reactions to sulfate (Tabacova 1986). Hydrogen sulfide can also be detoxified by methylation (EPA 1987a; Weisiger and Jakoby 1980). The proposed detoxification pathways most currently accepted for the metabolism of hydrogen sulfide are shown in Figure 3-2 and include oxidation and methylation, as well as the toxic pathways resulting from interactions with metalloproteins and disulfide-containing proteins.

The major metabolic pathway for hydrogen sulfide in the body is the oxidation of sulfide to sulfate, which is excreted in the urine (Beauchamp et al. 1984). The major oxidation product of sulfide is thiosulfate, which is then converted to sulfate; the primary location for these reactions is in the liver (Bartholomew et al. 1980).

Urinary thiosulfate levels were measured in volunteers exposed to 8, 18, or 30 ppm of hydrogen sulfide for 30–45 minutes and compared to levels in unexposed individuals at a pelt processing plant (Kangas and Savolainen 1987). Very little urinary thiosulfate was excreted in controls (2.9 µmol/mmol creatinine). The highest urinary thiosulfate levels among exposed individuals occurred 15 hours after exposure and decreased to control levels by 17 hours postexposure (Kangas and Savolainen 1987). Most absorbed hydrogen sulfide was already oxidized by 15 hours postexposure (Kangas and Savolainen 1987). This study was limited by the lack of summary data on exposed individuals and inadequate data regarding the numbers of subjects. Using perfused rat liver, Bartholomew et al. (1980) found that there was a rapid oxidation of ^{35}S-sulfide to sulfate. Furthermore, there was a decrease in thiosulfate released from the liver when nonlabelled thiosulfate was added to the perfusion system, suggesting that thiosulfate may act as an intermediate in the oxidation to sulfate (Bartholomew et al. 1980).

Japanese white rabbits exposed to 500–1,000 ppm hydrogen sulfide (the lethal concentration, for 14–30 minutes) had thiosulfate concentrations of 0.08 µM/mL in blood, 0.095 µM/g in lung, and 0.023 µM/g in brain (Kage et al. 1992). Although sulfide was not detected in blood or urine samples of rabbits exposed to a concentration of 100–200 ppm hydrogen sulfide for 60 minutes, thiosulfate levels were highest (1.2 µM/mL) 1–2 hours after exposure and could still be detected in urine 24 hours after exposure (Kage et al. 1992). Thiosulfate levels in blood peaked (0.061 µM/mL) immediately after exposure and were undetectable after 4 hours (Kage et al. 1992).

Figure 3-2. Metabolic Pathways of Hydrogen Sulfide*



*Adapted from Beauchamp et al. 1984

Evidence for the methylation of hydrogen sulfide comes primarily from *in vitro* studies of Sprague-Dawley rats' intestinal mucosa (Weisiger et al. 1980). Thiol *S*-methyltransferase catalyzed the methylation of hydrogen sulfide to methanethiol (CH_3SH). Methanethiol can act as a substrate for another methylation also catalyzed by thiol *S*-methyltransferase, yielding dimethylsulfide (CH_3SCH_3). The activity of thiol *S*-methyltransferase was widely distributed, with the greatest in cecal and colonic mucosa, liver, lung, and kidney, and was also found in other parts of the intestine and stomach, spleen, heart, and skeletal muscle. No enzyme activity was found in the feces. Although it has been postulated that methylation is a method of detoxification of hydrogen sulfide, a constituent of human flatus produced in the intestine, the extent to which the toxicity of exogenous hydrogen sulfide is attenuated by methylation is not known.

The interaction of hydrogen sulfide with metalloproteins was postulated because the mechanism of toxicity for hydrogen sulfide is the inhibition of cytochrome oxidase and thus, inhibition of the electron transport system. It appears that hydrogen sulfide interacts with other metalloproteins and may represent a detoxification pathway in some instances (Beauchamp et al. 1984). Reduction of disulfide bridges by hydrogen sulfide was suggested by Smith and Abbanat (1966), who found that mice were protected from lethal concentrations of hydrogen sulfide by the administration of oxidized glutathione. This protection was not afforded by the administration of reduced glutathione. The study authors believed that the disulfide linkage of the oxidized glutathione interacted with the hydrosulfide, which prevented the reaction of sulfide with other sites (Smith and Abbanat 1966). This is attributed to the polarizability of the disulfide bond. The nucleophilic sulfhydryl group of hydrogen sulfide reacts with the δ^+ of the disulfide bond, thus converting it to a less toxic product.

No studies were located regarding metabolism in humans or animals after oral, dermal, or other routes of exposure to hydrogen sulfide.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

The major metabolic pathway for hydrogen sulfide in the body is oxidation of sulfide to sulfate, with the sulfate being excreted in the urine (Beauchamp et al. 1984). Thiosulfate excretion was measured in volunteers exposed to 8, 18, or 30 ppm of hydrogen sulfide for 30–45 minutes and compared to that of unexposed individuals at a pelt processing plant (Kangas and Savolainen 1987). The study did not report

the summary results of all exposed individuals; however, data from one individual exposed to 18 ppm hydrogen sulfide for 30 minutes found urinary thiosulfate concentrations of approximately 2, 4, 7, 30, and 5 µM/mM creatinine at 1, 2, 5, 15, and 17 hours postexposure, respectively. The highest urinary thiosulfate levels among exposed individuals occurred 15 hours after exposure and dropped to control levels by 17 hours postexposure.

Kage et al. (1992) evaluated sulfide and thiosulfate levels in the blood and urine of Japanese white rabbits exposed to 100–200 ppm for 60 minutes and concluded that thiosulfate was a better marker for exposure since it could be detected immediately in the blood, but also was detectable in the urine 24 hours after exposure. In the blood, thiosulfate levels decreased from 0.061 µM/mL immediately following exposure to an undetectable amount after 4 hours (Kage et al. 1992). In urine samples from these same animals, thiosulfate levels were highest (1.2 µM/mL) 1–2 hours after exposure, but were still detectable after 24 hours of exposure at slightly higher level than that of control (Kage et al. 1992).

3.4.4.2 Oral Exposure

No studies were located regarding excretion in humans or animals after oral exposure to hydrogen sulfide.

3.4.4.3 Dermal Exposure

No studies were located regarding excretion in humans after dermal exposure to hydrogen sulfide.

Excretion of hydrogen sulfide was documented after dermal exposure in rabbits. Trunk fur of rabbits was clipped and left intact or abraded for exposure to hydrogen sulfide gas (unknown concentrations) for 1.5–2 hours; the animals then breathed clean air (Laug and Draize 1942). Evidence for the excretion of hydrogen sulfide by the rabbits was a sulfide reaction of the expired air with lead acetate paper (Laug and Draize 1942). Sulfides in the expired air were noted in one rabbit with intact skin after 7 minutes of exposure. This study was limited by the lack of measurement of exposure concentrations and the small number of animals used.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for

many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-3 shows a conceptualized representation of a PBPK model.

No PBPK models have been developed for hydrogen sulfide.

3.5 MECHANISMS OF ACTION

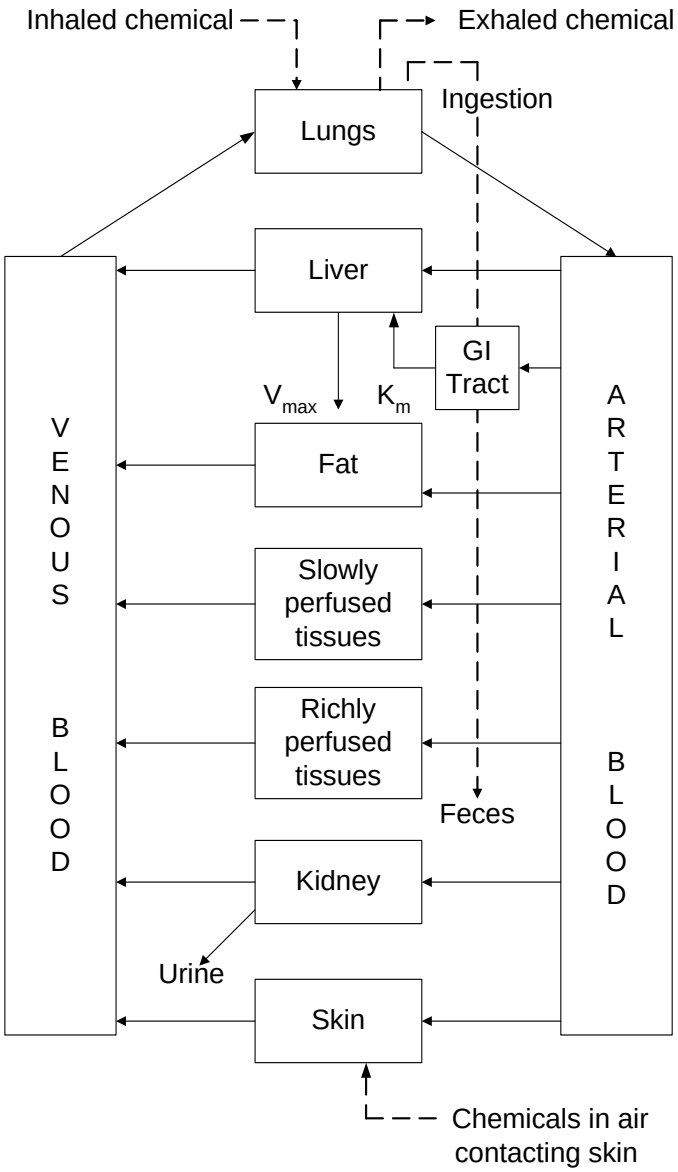
3.5.1 Pharmacokinetic Mechanisms

Hydrogen sulfide is primarily absorbed through the lungs. It can also be absorbed through the gastrointestinal tract and the skin. Hydrogen sulfide is widely distributed in the body after inhalation exposure. Based on analyses of tissues from humans who died after accidental exposure, sulfides have been detected in the liver, blood, brain, lungs, spleen, and kidneys. Hydrogen sulfide is metabolized by oxidation, methylation, and reaction with metalloproteins or disulfide-containing proteins. The major metabolic pathway for detoxification of hydrogen sulfide is oxidation of the sulfide to sulfate in the liver. Hydrogen sulfide is excreted primarily as sulfate in the urine.

3.5.2 Mechanisms of Toxicity

Exposure to hydrogen sulfide at concentrations of 500 ppm and greater causes an initial increase in the rate of respiration as a result of the stimulation of the carotid bodies, chemosensors associated with ventilatory control (Ammann 1986). Under normal conditions, these chemosensors stimulate ventilation of the lung during extreme cases in which a significant decrease in the partial pressure of oxygen in the arterial blood traveling to the head occurs (Ammann 1986). This action results in an increase in the number of impulses originating from the chemosensors to the respiratory center in the brain. The rate and depth of ventilation increases to the point of hyperpnea (rapid, deep breathing).

Figure 3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Direct inhibition of cellular enzymes has been postulated as one of many underlying mechanisms of toxicity of hydrogen sulfide (Beauchamp et al. 1984; Deng 1992). In particular, cytochrome oxidase, an enzyme involved in cellular oxidative processes and energy production, has been implicated. Inhibition of cytochrome oxidase is believed to disrupt the electron transport chain and to significantly impair oxidative metabolism, leading to anaerobic metabolism, severely decreased ATP production with curtailed cellular energy generation, and the generation of lactic acid. Nervous and cardiac tissues, which have the highest oxygen demand, are especially sensitive to the disruption of oxidative metabolism (Ammann 1986). In the central nervous system, this effect may result in death from respiratory arrest.

Inhibition of cytochrome oxidase by hydrogen sulfide is similar to that of cyanide (Smith and Gosselin 1979). Although the suggestion has been frequently made that the effects of hydrogen sulfide on nervous tissue are, as with cyanide, simply due to inhibition of oxidative metabolism, recent authors suggest that this is not the case. Reiffenstein et al. (1992) examined this issue and concluded that while treatment with hydrogen sulfide and anoxic conditions arrive at the same end point, there are pharmacological dissimilarities. Baldelli et al. (1993) investigated the mechanism of toxicity associated with hydrogen sulfide exposure (achieved by intravenous injection of sodium sulfide) and concluded that it resulted not from a direct toxicity on central nervous system neurons (i.e., a ‘cerebral necrosis’ due to poisoning of mitochondria respiration), but rather, from an indirect effect associated with a profound hypotension most likely due to cardiotoxicity. These authors emphasized the importance of immediate cardiopulmonary resuscitation as a way to prevent the delayed toxicity associated with hydrogen sulfide “knock-down” exposures.

An electrophysiological study of the effects of hydrogen sulfide on membrane and synaptic properties of dorsal raphe serotonergic cells in an *in vitro* rat brain-stem slice preparation has elucidated a possible mechanism of neurotoxicity of hydrogen sulfide (Kombian et al. 1993). These neurons are considered to play an important role in central nervous system control of respiratory rhythm. Hydrogen sulfide has been shown to produce two reversible, concentration-dependent effects on the resting membrane properties of the dorsal raphe neurons. Some neurons (14%) responded to hydrogen sulfide with an outward current accompanied by an increase in conductance, while 39% of the neurons responded with a rapid-onset depolarization corresponding to a weakly voltage-dependent inward current showing little or no change in conductance. In addition, 30% of the neurons displayed both types of responses. Finally, 18% of the neurons were unresponsive to hydrogen sulfide. The outward current induced by hydrogen sulfide was demonstrated to be caused by an elevated conductance to potassium, whereas the hydrogen

sulfide-induced inward current is carried by calcium ions. However, the mechanism of calcium ion entry is not clear.

Hydrogen sulfide was shown to inhibit, in a concentration-dependent fashion, all components of the complex evoked synaptic responses of the dorsal raphe serotonergic neurons (Kombian et al. 1993). This effect was rapid and reversible, and involved both pre- and postsynaptic mechanisms. Similar effects of hydrogen sulfide on brain hippocampal CA1 neurons have been reported. The electrophysiological effects of hydrogen sulfide are comparable to those elicited by anoxia. The neuronal action of hydrogen sulfide may involve an interaction with free thiols and disulfide bonds present in most membrane proteins. Collectively, the electrophysiology data suggest a possible role of the effects of hydrogen sulfide on synaptic and membrane properties of the dorsal raphe serotonergic neurons of the brain stem in the cessation of respiratory drive following acute hydrogen sulfide exposure.

Inhibition of monoamine oxidase has been proposed as a possible mechanism underlying the hydrogen sulfide–mediated disruption of neurotransmission in brain stem nuclei controlling respiration (Warenycia et al. 1989a). Administration of sodium hydrosulfide, an alkali salt of hydrogen sulfide, has been shown to increase brain catecholamine and serotonin levels in rats. It has also been suggested that persulfide formation resulting from sulfide interaction with tissue cystine and cystinyl peptides may underlie some aspects of hydrogen sulfide neurotoxicity, including inhibition of monoamine oxidase (Warenycia et al. 1990).

3.5.3 Animal-to-Human Extrapolations

The toxicokinetic disposition of hydrogen sulfide in humans is not understood. However, available toxicity and toxicokinetic data indicate that hydrogen sulfide can be readily absorbed through the lung and, to a lesser and clinically irrelevant extent, through the gastrointestinal tract and skin. Although the metabolism of hydrogen sulfide has been characterized in animals, there are limited data to suggest that the metabolism of hydrogen sulfide may be in part similar in humans. For instance, human data indicate that hydrogen sulfide is oxidized to sulfate and thiosulfate and excreted in the urine. Neurotoxicity induced by hydrogen sulfide has been observed in experimental animals and humans.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997b). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were identified on the potential for hydrogen sulfide to disrupt the function of the neuroendocrine axis.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient

tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

There is little information in the available literature to judge the impacts of exposure to hydrogen sulfide on infants and children, however; it is likely that the same toxicity seen in adults will be seen in children. Acute exposures to hydrogen sulfide have caused death in adolescents as well as adults (Allyn 1931; Hagley and South; Morse et al. 1981). Gaitonde et al. (1987) reported on a toxic encephalopathy in a 20-month-old child who had long-term exposure to pollutants generated from “a burning tip” from a coal mine. Hydrogen sulfide levels as high as 0.6 ppm had been measured in the family’s housing tract; however, no information was provided about the level of other combustion products that might have been produced by the same source.

Several studies have examined the reproductive and developmental toxicity of inhaled hydrogen sulfide in animals. Saillenfait et al. (1989) observed no fetal effect in a dose range-finding developmental study in which pregnant Sprague-Dawley dams were exposed to 150 ppm hydrogen sulfide for 6 hours/day from gestation day 6 until gestation day 20, even though the dams showed significant body weight loss at this dose. Hayden et al. (1990b) found a dose-related increase in parturition time in animals exposed to 20, 50, or 75 ppm hydrogen sulfide for 7 hours/day from gestation day 6 until postpartum day 21 and noted that at the extreme end of the range (i.e., 200 minutes), viability was decreased to about 70%. This study also found delays in pinna detachment and hair development; however, for both effects the delay was longer at the lower concentration (i.e., no dose-related increase in effects was observed).

Hannah and Roth (1991) exposed timed pregnant dams (and their pups) from day 5 postcoital until postnatal day 21 to either 20 or 50 ppm of hydrogen sulfide for 7 hours/day and found severe alterations in the architecture and growth patterns of the Purkinje cell dendritic fields at both doses leading these

authors to conclude that exposure to low concentrations of hydrogen sulfide place “developing neurons...at risk of severe deficits.”

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to hydrogen sulfide are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by hydrogen sulfide are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 “Populations That Are Unusually Susceptible”.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Hydrogen Sulfide

The most frequently used biomarker of hydrogen sulfide exposure is urinary thiosullfate levels (Milby and Baselt 1999). Thiosulfate is an oxidation product of hydrogen sulfide metabolism and is not specific to hydrogen sulfide metabolism. Ingestion of food or water with a high sulfur content can also increase urinary thiosulfate concentrations (Milby and Baselt 1999). An increase in urinary thiosulfate levels were observed in individuals exposed to 8, 18, or 30 ppm hydrogen sulfide for 30–45 minutes (Kangas and Savolainen 1987). The urinary thiosulfate levels peaked approximately 15 hours after exposure. In a subject exposed to 18 ppm for 30 minutes, the peak urinary thiosulfate concentration at 15 hours was 30 µmol/mmol creatinine; 17 hours after exposure, the urinary thiosulfate levels were similar to non-exposed individuals (mean concentration of 2.9 µmol/mmol creatinine). A quantitative relationship between hydrogen sulfide exposure levels and urinary thiosulfate levels has not been established.

Measurement of blood sulfide levels has also been proposed as a biomarker of exposure (Jappinen and Tenhunen 1990). This has limited clinical value because the blood samples must be collected within 2 hours of exposure (Jappinen and Tenhunen 1990). As with urinary thiosulate levels, a relationship between airborne hydrogen sulfide levels and blood sulfide levels has not been established.

Jappinen and Tenhunen (1990) also investigated the use of alterations in blood heme metabolism as a possible biomarker of hydrogen sulfide exposure. The activities of the enzymes of heme synthesis, i.e., delta-aminolaevulinic acid synthase (ALA-S) and heme synthase, were examined in 21 cases of acute hydrogen sulfide toxicity in Finnish pulp mill and oil refinery workers exposed to 20–200 ppm hydrogen sulfide for periods ranging from approximately 1 minute up to 3.5 hours. Several subjects lost consciousness for up to 3 minutes. Activities of delta-aminolaevulinic acid synthase and heme synthase were decreased after exposure to hydrogen sulfide. However, the changes in heme metabolism are not specific for hydrogen sulfide, and other sulfur-containing compounds, such as methyl mercaptan, can produce similar effects.

3.8.2 Biomarkers Used to Characterize Effects Caused by Hydrogen Sulfide

Hydrogen sulfide-specific biomarkers of effect have not been identified. Potential biomarkers for neurological effects of hydrogen sulfide include indices of cortical, hippocampal, brain stem, basal ganglia, and diencephalon dysfunction. An oil-field worker who became unconscious following exposure to hydrogen sulfide had a diminished vibration sense, delayed visual reaction times, abnormal balance with eyes closed, slow blink reflex latency, impaired verbal and visual recall, and decreased cognitive performance (Kilburn 1993). Cortical function tests revealed deficits in verbal abstraction, attention, and short-term retention in a hydrogen sulfide-poisoned patient (Stine et al. 1976). A 5-year neuro-psychological re-examination of patients who lost consciousness after hydrogen sulfide exposure revealed neurological impairment (Tvedt et al. 1991b); memory and motor function were most affected. Such neurological effects are not specific for hydrogen sulfide and could indicate exposure to other neurotoxic substances.

3.9 INTERACTIONS WITH OTHER CHEMICALS

In a group of Belgian viscose rayon workers exposed to 0.14 or 6.4 ppm of hydrogen sulfide and at least 26 mg/m^3 of carbon disulfide, the incidence of eye irritation was significantly higher in all hydrogen sulfide-exposed workers than in unexposed controls (Vanhoorne et al. 1995). Control for confounders such as cigarette smoke was not performed (Vanhoorne et al. 1995). Simultaneous exposure of Sprague-Dawley rats to 500 ppm of carbon disulfide and 50 ppm of hydrogen sulfide 5 days/week, for 25 weeks, had no interactive effect on sensory tail nerve conduction velocities (SNCV) or motor tail nerve conduction velocities (MNCV) (Gagnaire et al. 1986). Additionally, the amount of 2-thio-thiazo-lidine-4-carboxylic acid, a urinary metabolite of carbon disulfide excreted in urine after exposure to carbon disulfide, was unaffected by hydrogen sulfide exposure (Gagnaire et al. 1986). In a series of reproductive and developmental studies in which albino rats were exposed to hydrogen sulfide and carbon disulfide, both pre- and postimplantational lethality as well as developmental anomalies of the genito-urinary and skeletal systems were reported (Barilyak et al. 1975). However, in some cases, these effects occurred in conjunction with maternal toxicity. It is not clear whether the reported concentration (10 mg/m^3) to which the animals were exposed includes both hydrogen sulfide and carbon disulfide or represents individual concentrations of each chemical.

There appears to be some evidence that ethanol can increase the effects of hydrogen sulfide. In six cases, less hydrogen sulfide was needed for toxic effects to be observed when workers had consumed alcohol 16–24 hours earlier (Poda 1966).

Much of the occupational data on hydrogen sulfide comes from studies of pulp and paper mill workers who were exposed to other compounds in addition to hydrogen sulfide. An increase in chronic or recurrent headache was noted in Finnish pulp workers who were exposed simultaneously to hydrogen sulfide, methyl mercaptans, and sulfur dioxide (Kangas et al. 1984). Peak concentrations of the chemicals, up to 20 ppm hydrogen sulfide, were believed to be responsible for the occurrence of the symptoms, rather than the lower mean concentrations. A respiratory survey of almost 2,000 Canadian pulp and paper mill workers did not show any increases in the prevalence of respiratory symptoms or pulmonary function abnormalities among exposed workers (Chan-Yeung et al. 1980). Mean exposure concentrations of toxicants measured in this study were 0.05 ppm hydrogen sulfide, 0.3 ppm sulfur dioxide, 8.3 ppm carbon monoxide, 0.8 ppm total particulates, and <0.05 ppm chlorine.

No changes in body weight or microscopic changes in respiratory tract, eye, or visceral organs were noted in crossbred pigs inhaling 2 ppm of hydrogen sulfide and 50 ppm of ammonia continuously for 19 days when compared to controls (Curtis et al. 1975). The toxicity of hydrogen sulfide after dermal exposure was found to be enhanced by dermal exposure to ammonia (Laug and Draize 1942).

Male Wistar rats were administered 330 or 660 mg/kg of ethanol intraperitoneally 30 minutes before being exposed to 800 ppm of hydrogen sulfide for a maximum of 20 minutes, which was a potentially fatal hydrogen sulfide exposure (Beck et al. 1979). Mean times to unconsciousness in animals that were exposed to hydrogen sulfide with ethanol pretreatment at either of these dose levels were approximately 35% less than times to unconsciousness without ethanol pretreatment (Beck et al. 1979). The clinical relevance of these findings, which used potentially fatal doses of both ethanol and hydrogen sulfide, is unclear.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to hydrogen sulfide than will most persons exposed to the same level of hydrogen sulfide in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of hydrogen sulfide, or compromised

function of organs affected by hydrogen sulfide. Populations who are at greater risk due to their unusually high exposure to hydrogen sulfide are discussed in Section 6.7, Populations With Potentially High Exposures.

Some asthmatics exposed to 2 ppm hydrogen sulfide for 30 minutes had changes in pulmonary function tests indicative of bronchial obstruction, although the exposed group as a whole did not show a statistically significant change in these parameters (Jappinen et al. 1990). Asthmatics have also been found to have a worsening of their condition upon exposure to odors (Shim and Williams 1986). Although this has not been tested with exposure to hydrogen sulfide, it might be reasonably anticipated due to the malodorous quality of hydrogen sulfide gas. These findings suggest that some asthmatics may be more sensitive to hydrogen sulfide than the general population.

Evidence from a number of studies suggests that hydrogen sulfide, endogenously produced by bacteria in the digestive tract, may play a role in the etiology of ulcerative colitis (Babidge et al. 1998; Pitcher and Cummings 1996; Roediger et al. 1997). It is unclear whether patients are affected due to the excess production of hydrogen sulfide or the inability to detoxify it as effectively as controls. Irrespective of mechanism, it seems likely that individuals already suffering from hydrogen sulfide-associated toxicity will be at higher risk from further hydrogen sulfide exposures. Ulcerative colitis is usually found in adults, so children are less susceptible.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to hydrogen sulfide. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to hydrogen sulfide. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to hydrogen sulfide:

Agency for Toxic Substances and Disease Registry. 1994. Hydrogen sulfide. Managing hazardous materials incidents. Volume III. Medical management guidelines for acute chemical exposures. Atlanta, GA: Agency for Toxic Substances and Disease Registry.

Ellenhorn MJ. 1997. Hydrogen sulfide. In: Ellenhorn's medical toxicology: Diagnosis and treatment of human poisoning. 2nd edition. Baltimore, MD: Williams and Wilkins.

Hall AH. 1996. Systemic asphyxiants. In: Rippe JM, Irwin RS, Fink MP, et al. eds. Intensive care medicine. 3rd edition. Boston, MA: Little, Brown, and Company.

There is no widely accepted antidote for hydrogen sulfide poisoning. Treatment consists of supportive measures such as evaluating and supporting airway, breathing, and circulation (Agency for Toxic Substances and Disease Registry 1994). A number of case reports of individuals exposed to high concentrations of hydrogen sulfide resulting in unconsciousness suggest that administration of sodium nitrite and/or amyl nitrate may be an effective antidote for hydrogen sulfide poisoning (Hall 1996; Hall and Rumack 1997; Hoidal et al. 1986; Stine et al. 1976). The nitrate induces the formation of methemoglobin, which has a higher affinity for hydrogen sulfide than does cytochrome oxidase. Hyperbaric oxygen therapy is controversial, but it may be effective for patients not treated successfully by other measures (Agency for Toxic Substances and Disease Registry 1994).

There are no pediatric-specific methods for reducing toxic effects.

3.11.1 Reducing Peak Absorption Following Exposure

There are no specific methods available to reduce the absorption of hydrogen sulfide following exposure. Supportive treatment includes artificial respiration if respiration is depressed; administration of oxygen; and standard medical treatment for eye irritation, pulmonary edema, seizures, and hypotension (Sorokin 1993).

3.11.2 Reducing Body Burden

There are no known methods for reducing the body burden of hydrogen sulfide, although adopting a diet low in sulfur-containing, exogenously acquired foods, e.g., milk and cheese, has been shown to reduce the endogenous production of hydrogen sulfide (Roediger et al. 1997).

The major metabolic pathway of hydrogen sulfide is the oxidation of the sulfide to sulfate in the liver (Beauchamp et al. 1984). Methylation also serves as a detoxification route. Hydrogen sulfide is excreted primarily as sulfate (either as free sulfate or as thiosulfate) in the urine.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Hydrogen sulfide inhibits mitochondrial cytochrome oxidase, resulting in disruption of the electron transport chain and impairing oxidative metabolism. Nervous and cardiac tissues, which have the highest oxygen demand (e.g., brain and heart), are especially sensitive to disruption of oxidative metabolism (Ammann 1986; Hall 1996).

Nitrites such as amyl and sodium nitrites have been used in the treatment of hydrogen sulfide poisoning, and the mechanism of therapeutic action may involve the prevention or reversal of cytochrome oxidase inhibition (Ellenhorn 1997; Hall 1996; Hoidal et al. 1986; Osbern and Crapo 1981; Reiffenstein et al. 1992). It has been postulated that nitrites induce methemoglobin, which inactivates sulfide, thereby preventing cytochrome oxidase inhibition and reactivating aerobic respiration (Ellenhorn 1997; Hall 1996). There is antidotal evidence to suggest that this is an effective treatment in cases of exposure to high concentrations of hydrogen sulfide (Hall 1996; Hall and Rumack 1997; Hoidal et al. 1986; Stine et al. 1976).

Oxygen treatment may be used after hydrogen sulfide poisoning, although its use is somewhat controversial (Ellenhorn 1997; Ravizza et al. 1982). Smith et al. (1976) found that oxygen was not useful as an antidote to hydrogen sulfide poisoning in mice. High intracellular oxygen pressure may result in nonenzymatic oxidation of cytochrome oxidase, and oxygen may release sulfide from cytochrome oxidase binding by a concentration effect (Ravizza et al. 1982). Hyperbaric oxygen therapy has been suggested for cases not responding to supportive care and nitrite treatment, but its clinical efficacy has not yet been determined (Ellenhorn 1997; Hall 1996).

In one case report (Schneider et al. 1998) where an individual suffered long-term (4 years later) neuropsychological sequelae from a “knock-down” exposure to hydrogen sulfide, treatment with two drugs, Ritalin and Cyclert, partially alleviated some of the observed deficits in cognitive function and general cognition; these drugs enhance dopaminergic functioning. However, more examples of the efficacy of this treatment are required.

3.12 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether

adequate information on the health effects of hydrogen sulfide is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of hydrogen sulfide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

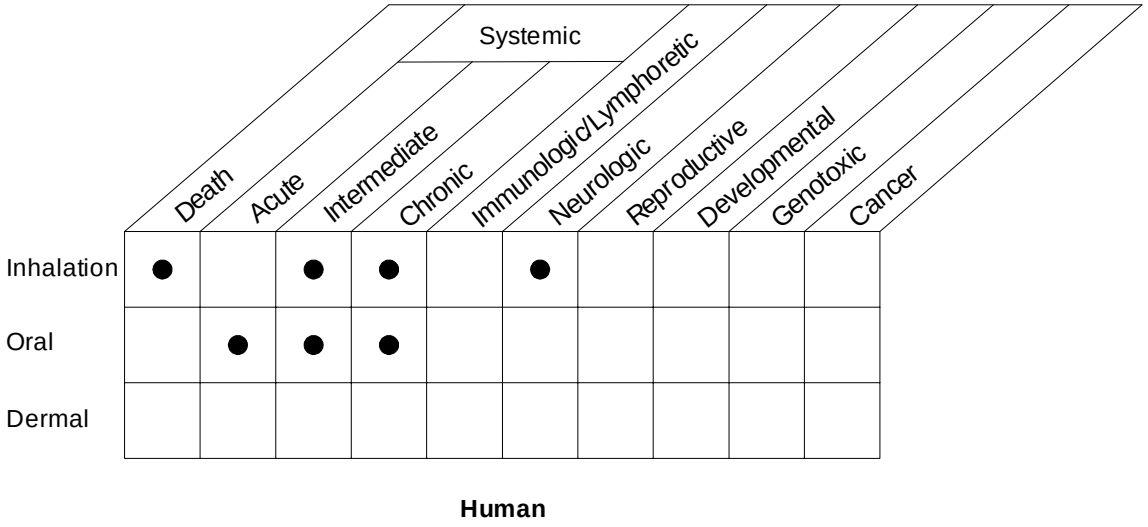
3.12.1 Existing Information on Health Effects of Hydrogen Sulfide

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to hydrogen sulfide are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of hydrogen sulfide. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

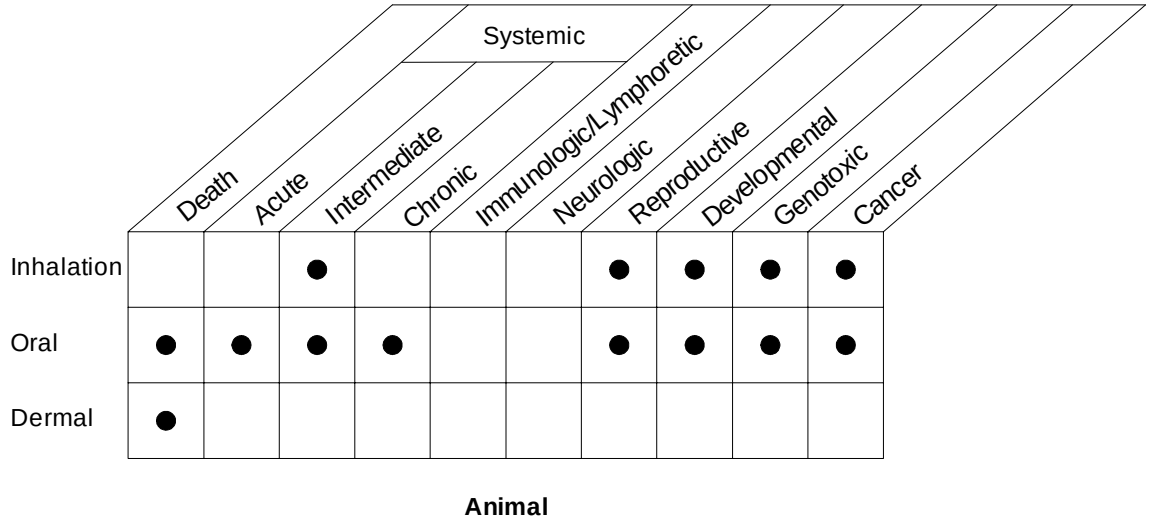
3.12.2 Identification of Data Needs

Acute-Duration Exposure. There are numerous case reports of human fatalities (Adelson and Sunshine 1966; Allyn 1931; Breysse 1961; Campanya et al. 1989; Deng and Chang 1987; Freireich 1946; Hagley and South; Morse et al. 1981; Osbern and Crapo 1981; Parra et al. 1991) or survivors who developed immediate as well as delayed neurological effects (Deng and Chang 1987; Kilburn 1993, 1997; Krekel 1964; McDonald and McIntosh 1951; Milby 1962; Schneider 1998; Spolyar 1951) following acute-duration hydrogen sulfide inhalation exposure. Estimates of exposure concentrations were not often reported in these studies. Cardiac arrhythmia has also been reported in workers exposed to

Figure 3-4. Existing Information on Health Effects of Hydrogen Sulfide



Human



Animal

● Existing Studies

hydrogen sulfide (Krekel 1964). Experimental exposure studies in which subjects were exposed to hydrogen sulfide for 15–30 minutes did not identify any respiratory or cardiovascular effects in healthy subjects at 5 or 10 ppm (Bhambhani and Singh 1991; Bhambhani et al. 1994, 1996a). Pulmonary function tests were normal in workers exposed to up to 10 ppm hydrogen sulfide (Jappinen et al. 1990). Evidence of bronchial obstruction was observed in 2 of 10 asthmatics exposed to 2 ppm of hydrogen sulfide, although the group as a whole had no significant change in these parameters (Jappinen et al. 1990). Additionally, studies are needed to assess whether asthmatic subjects are a sensitive subpopulation. Because hydrogen sulfide gas is an eye irritant (Ahlborg 1951; Luck and Kay 1989), such studies should also monitor ocular effects. Additional studies of the delayed consequences of acute exposures are also needed.

Acute-duration inhalation studies of hydrogen sulfide in animals have reported death (Beck et al. 1979; Khan et al. 1990; Lopez et al. 1989; Nagata et al. 1990; Prior et al. 1988, 1990; Smith and Gosselin 1964; Tansy et al. 1981), respiratory (Brenneman et al. 2002; Green et al. 1991; Khan et al. 1990; Kohno et al. 1991; Lopez et al. 1987, 1988a, 1988b; Prior et al. 1990), cardiovascular (Higuchi and Fukamachi 1977; Kohno et al. 1991; Kosmider et al. 1967), immunological/lymphoreticular (Khan et al. 1991), and neurological effects (Beck et al. 1979; Haider et al. 1980; Higuchi and Fukamachi 1977; Kosmider et al. 1967; Lopez et al. 1988b; Struve et al. 2001). Additional acute-duration inhalation animal studies would be useful to further define any direct cardiovascular effects of hydrogen sulfide as opposed to those due to hypoxia. The available data on the acute toxicity of inhaled hydrogen sulfide were sufficient for derivation of an acute-duration inhalation MRL.

Data are not sufficient for the development of an acute-duration oral MRL. The only oral study of hydrogen sulfide is a study in which a diarrheic digestive disorder was observed in pigs fed hydrogen sulfide at 15 mg/kg/day for "a few days" (Wetterau et al. 1964). Acute dermal exposure of animals has resulted in death (Laug and Draize 1942). In addition to a lack of route-specific toxicity data, insufficient pharmacokinetic data are available to support the identification of target organs across routes of exposure. However, although oral and dermal data regarding the effects of hydrogen sulfide are very limited, human exposure would be expected to be principally by inhalation.

Intermediate-Duration Exposure. Intermediate-duration studies in humans are fairly limited and virtually all are complicated by exposures to other chemicals as well as rarely being accompanied with adequate exposure assessment. Additional epidemiologic studies, particularly prospective or case-

control, of populations exposed environmentally to various levels of hydrogen sulfide (where other pollutants are monitored and ideally, do not vary) are needed.

A series of 90-day inhalation studies in rats (CIIT 1983b, 1983c) reported significantly decreased body weights in Sprague-Dawley female rats at 80 ppm, but not in male Sprague-Dawley (CIIT 1983c) nor in either sex of F-344 rats (CIIT 1983b). Although CIIT (1983b, 1983c) did not report increases in the occurrence histological lesions, a re-examination of the histological slides from this study (Dorman et al. 2004) found increases in the incidence of nasal (olfactory neuron loss) and lung (bronchiolar epithelial hypertrophy and hyperplasia) lesions at 30 ppm and higher. In a companion study with $B6C3F_1$ mice, a significant increase in the incidence of inflammation of the nasal mucosa was observed at a dose level of 80 ppm but not at 30.5 ppm. Brenneman et al. (2000) identified a NOAEL and LOAEL for nasal effects (loss of olfactory neurons) in Sprague-Dawley rats exposed to 10 and 30 ppm, respectively, for 10 weeks. This study was used as the basis of an intermediate-duration inhalation MRL for hydrogen sulfide.

No histopathological effects were found in respiratory tract tissues or organs when pigs were exposed to 8.5 ppm hydrogen sulfide continuously for 17 days (Curtis et al. 1975). Additional effects reported in rats following inhalation exposure to hydrogen sulfide include increased glucose in lactating rats (Hayden et al. 1990a), increased liver cholesterol in female rats exposed during gestation and lactation (Hayden et al. 1990b), and weight loss in pregnant rats (Saillenfait et al. 1989).

The only oral study of hydrogen sulfide is a study in pigs in which decreased body weights were observed in pigs fed hydrogen sulfide in the diet at 6.7 mg/kg/day for 105 days (Wetterau et al. 1964). No effects were observed at a dose of 3.1 mg/kg/day. However, because this study lacks details and there are no supporting data, no intermediate-duration MRL was derived. Additional intermediate-duration oral studies of hydrogen sulfide are needed to provide support for this study.

No intermediate-duration dermal studies of hydrogen sulfide were identified. As significant human dermal exposure to hydrogen sulfide is unlikely, dermal exposure studies should not be a high priority. However, no pharmacokinetic data are available that might support the identification of target organs across routes of exposures in the absence of route-specific toxicity data.

Chronic-Duration Exposure and Cancer. A study of workers exposed to hydrogen sulfide at concentrations that often exceeded 20 ppm reported slight irritation of the mucous membranes, fatigue, loss of appetite, headache, irritability, poor memory, and dizziness (Ahlborg 1951). Pulp industry

workers exposed to 8-hour TWA concentrations of 0.05–5.2 ppm hydrogen sulfide had no signs of clinical anemia but did show decreases in ALA-S, Heme-S, and ALA dehydratase activities, as well as erythrocyte protoporphyrin (Tenhunen et al. 1983). This study was confounded by workers' exposure to other compounds such as methyl mercaptan and dimethylsulfide, inadequately described controls, and an absence of statistical analysis. A study of persons living near a paper mill who were exposed to hydrogen sulfide showed increased eye irritation and some respiratory effects compared to nonexposed individuals; however, they were also exposed to methyl mercaptan and sulfur dioxide (Jappinen et al. 1990). There was no increase in cancer incidence noted in a residential cohort study of persons living downwind from natural gas refineries (Schechter et al. 1989), but an increased risk of nasal cancers was found in a population residing in a location of high geothermal activity (Bates et al. 1998).

Additional chronic-duration studies of hydrogen sulfide, including studies of the carcinogenic potential of hydrogen sulfide in humans and animals by any route of exposure, have not been performed. Follow-up epidemiological studies of populations environmentally exposed to hydrogen sulfide due to proximity of pulp mills, sour gas plants, or geothermal energy sources are needed, but only if they are accompanied by adequate exposure measurements. As limited genotoxicity studies suggest that hydrogen sulfide is unlikely to be a carcinogen, lifetime carcinogenicity studies in animals should not be a high priority. In the absence of route-specific toxicity data and route-specific pharmacokinetic data, it is not possible to identify target organs across routes of exposure.

Genotoxicity. No mutagenicity was observed in Ames assays using *Salmonella typhimurium* strains TA97, TA98, and TA100, either with or without S9 liver fractions from male Syrian golden hamsters or Sprague-Dawley rats (EPA 1984). Specific concentrations of hydrogen sulfide gas were limited because of its solubility in ethanol, which was the test solvent. The highest dose that could be obtained was 1,750 µg/plate. Other studies using hydrogen sulfide in the gaseous state would be useful for testing higher doses.

Reproductive Toxicity. The findings in two studies (Hemminki and Niemi 1982; Xu et al. 1998) that exposures to hydrogen sulfide are associated with an increased risk of spontaneous abortion warrants further investigation. A well-designed case-control study is needed in which exposure is well characterized in order to ascertain whether this is indeed an effect of concern or merely an anomaly. Additional epidemiologic studies of other reproductive effects would also be useful. No treatment-related histopathological changes were found in the male or female reproductive organs of rats (CIIT 1983b, 1983c) or mice (CIIT 1983a) exposed to hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days or in

rats exposed to 80 ppm hydrogen sulfide 6 hours/day, 7 days/week for 60–70 days (Dorman et al. 2000). The Dorman et al. (2000) study also found no exposure-related alterations in fertility, late resorptions or stillbirths, litter size, or length of gestation. A multilitter or multigeneration study in several animal species after exposure to hydrogen sulfide by inhalation is needed to further evaluate the reproductive potential of hydrogen sulfide.

Developmental Toxicity. No studies were located regarding developmental effects in humans following hydrogen sulfide exposure.

Developmental effects were not observed in rats exposed to hydrogen sulfide by inhalation at concentrations that resulted in maternal body weight loss (Saillenfait et al. 1989), increased maternal blood glucose levels (Hayden et al. 1990a), or increased cholesterol content of the maternal liver (Hayden et al. 1990b). Purkinje cell path length in offspring of exposed rats was increased compared to controls (Hannah and Roth 1991). Changes in amino acid levels (Hannah et al. 1989, 1990) and serotonin and epinephrine levels (Skrajny et al. 1992) in the brain were found in the offspring of rats exposed by inhalation to hydrogen sulfide during gestation. No alterations in performance on neurobehavioral tests were observed in the offspring of rats exposed to up to 80 ppm 6 hours/day, 7 days/week during gestation and lactation (the pups were also exposed on postnatal days 5–18) (Dorman et al. 2000). Studies regarding the developmental toxicity of hydrogen sulfide following oral or dermal exposure were not located.

Immunotoxicity. Immunological effects infrequently observed after human hydrogen sulfide exposure appear to result from infection due to the aspiration or ingestion of manure or vomit (Osbern and Crapo 1981). No treatment-related histopathological changes were found in the spleen or lymph nodes of rats (CIIT 1983b, 1983c) or mice (CIIT 1983a) exposed to hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days. Although the number of pulmonary alveolar macrophage cells was not influenced by hydrogen sulfide exposure, the number of viable cells was significantly decreased with exposure to 400 ppm (Khan et al. 1991). When pulmonary alveolar macrophage cells were treated with Zymosan to stimulate respiration rates, there was no stimulation of respiration in cells from animals exposed to 200 or 400 ppm of hydrogen sulfide for 4 hours (Khan et al. 1991). Immunological effects have not been studied in humans or animals following oral or dermal exposure to hydrogen sulfide.

Additional studies of immune function in animals exposed to hydrogen sulfide by inhalation are needed. A bacterial and/or viral challenge study would be especially useful to determine whether exposure to hydrogen sulfide increases susceptibility to infection.

Neurotoxicity. The nervous system is a target organ for hydrogen sulfide. Effects of acute inhalation exposure in humans include nausea, headaches, delirium, disturbed equilibrium, poor memory, loss of consciousness, tremors, and convulsions (Arnold et al. 1985; Deng and Chang 1987; Krekel 1964; McDonald and McIntosh 1951; Milby 1962; Spolyar 1951). Acute effects observed in animals include fatigue, somnolence (Haider et al. 1980), and loss of consciousness (Kosmider et al. 1967). Limited data from chronically exposed workers indicate that loss of appetite, fatigue, poor memory, dizziness, and irritability may result (Ahlborg 1951; Krekel 1964). Studies in rats have shown decreases in performance of discriminated avoidance tasks after exposure to hydrogen sulfide (Higuchi and Fukamachi 1977). The potential neurotoxicity of hydrogen sulfide following oral or dermal exposures has not been characterized. The transplacental neurological effects of hydrogen sulfide exposure are unknown. There is no reason to suspect that the neurotoxic effects observed after hydrogen sulfide exposure are species-specific, and insufficient data are available to determine whether effects are route-specific. Well-designed studies investigating neurotoxic effects in animals following oral or dermal exposure and chronic neurotoxic effects after inhalation exposure are needed to determine the effects that might be seen in exposed humans. Additionally, there is antidotal evidence that some individuals experience permanent or persistent neurological symptoms, such as memory loss, after acute exposures to high concentrations of hydrogen sulfide. Studies are needed to confirm these reports and determine if acute exposure to hydrogen sulfide can result in permanent neurological damage.

Epidemiological and Human Dosimetry Studies. Published reviews have addressed the duration of exposure and concentrations of hydrogen sulfide resulting in death and serious effects in humans (Beauchamp et al. 1984; EPA 1978; NIOSH 1977a; WHO 1981). The limited chronic-duration epidemiological studies (Ahlborg 1951; Jappinen et al. 1990; Schechter et al. 1989; Tenhunen et al. 1983) have identified approximate exposure concentrations, but exposure assessment was not sufficient to divide the study population into more than one exposure group. Epidemiology studies examining the potential effects of chronic inhalation exposure to various hydrogen sulfide concentrations are needed. There are known populations that have unusually high exposure to hydrogen sulfide.

Biomarkers of Exposure and Effect.

Exposure. Both blood sulfide concentrations (Jappinen and Tenhunen 1990) and urinary thiosulfate concentrations (Kage et al. 1992; Kangas and Savolainen 1987) have been proposed as indicators of hydrogen sulfide exposure. Obtaining background levels of blood sulfide in a population should not be problematic, although blood samples to determine sulfide concentrations must be obtained within 2 hours of exposure to hydrogen sulfide. Similarly, urinary thiosulfate levels can be obtained for the background population. Further study is needed to correlate airborne exposure concentrations with blood sulfide and thiosulfate levels. Additional alterations in heme synthesis enzymes (delta-aminolaevulinic acid synthase and heme synthase) have been proposed as possible biomarkers of exposure (Jappinen and Tenhunen 1990). These effects are not specific for hydrogen sulfide, and further study is needed to correlate these effects with blood sulfide and urinary thiosulfate levels.

Effect. No hydrogen-sulfide-specific biomarkers of effect have been identified. Neurological indices are also used as biomarkers of effect for hydrogen sulfide (Gaitonde et al. 1987; Kilburn 1993; Stine et al. 1976; Tvedt et al. 1991b). It is unlikely that a hydrogen-sulfide-specific biomarker of effect will be identified based on nonspecific effects that have been observed in humans and animals exposed to hydrogen sulfide and the mechanistic similarity between cyanide and hydrogen sulfide. Additional data are needed to identify a collection of symptoms that could reasonably characterize hydrogen sulfide exposure.

Absorption, Distribution, Metabolism, and Excretion. Hydrogen sulfide is absorbed through the lungs and can be absorbed in minor quantities through the gastrointestinal tract and intact skin (Kohno et al. 1991; Laug and Draize 1942; Wetterau et al. 1964). Hydrogen sulfide is also produced endogenously in many tissues (e.g., liver, kidney, and heart) as a break-down product of cysteine metabolism. Thus, hydrogen sulfide is widely distributed in the body. Sulfides have been found in the heart, liver, blood, brain, lungs, spleen, and kidneys of humans who died after accidental inhalation exposure (Kohno et al. 1991). However, there are no studies that have tracked the quantitative absorption or endogenous production of hydrogen sulfide nor quantified the differences in its distribution in the various tissues to follow absorption of an external dose. No data are available on distribution after oral or dermal exposure to hydrogen sulfide.

Hydrogen sulfide is metabolized through three pathways: oxidation, methylation, and reactions with metalloproteins or disulfide-containing proteins (Beauchamp et al. 1984). Although the major metabolic pathway for detoxification is oxidation of the sulfide to sulfate in the liver, methylation also serves to detoxify hydrogen sulfide (EPA 1987a; Weisiger and Jakoby 1980). The major oxidation product of hydrogen sulfide is thiosulfate, which is then converted to sulfate and excreted in the urine (Bartholomew et al. 1980; Kage et al. 1992; Kangas and Savolainen 1987). The primary location for the oxidation reaction is the liver (Bartholomew et al. 1980).

The qualitative data on the absorption, distribution, metabolism, and excretion of hydrogen sulfide in humans and animals are well known; quantitative data are generally lacking. Additional studies in animals that provide quantitative toxicokinetic data are needed.

Comparative Toxicokinetics. PBPK models have not been developed to compare the toxicokinetics of hydrogen sulfide in humans and animals. Studies providing quantitative data necessary to develop PBPK models would be useful.

Methods for Reducing Toxic Effects. Other than removing the subject from exposure, there is no specific method to reduce the absorption of hydrogen sulfide. There are no known methods for reducing the body burden of hydrogen sulfide, although reducing the intake of sulfhydryl-containing amino acids has been shown to reduce endogenous production. Amyl and sodium nitrites have been used as antidotes for hydrogen sulfide. Oxygen treatment, which may result in nonenzymatic oxidation of cytochrome oxidase, may also be used in the treatment of hydrogen sulfide poisoning (Hall 1996; Ravizza et al. 1982).

There is a need to develop an antidote for hydrogen sulfide poisoning, especially since it has a high knock-down potency. Additional research into the safe use of oxygen as an antidote for hydrogen sulfide poisoning is needed. Studies examining methods to enhance the oxidation or methylation of hydrogen sulfide to increase the elimination might also be useful. Further studies of the efficacy of drugs such as Retalin and Cyclert to treat the long-term neuropsychological effects of a knock-down exposure are needed.

Children's Susceptibility. There is only limited information available by which to assess the potential toxicity of hydrogen sulfide to children and infants. Several case reports suggest that adolescents respond much like adults to high dose acute exposures (Allyn 1931; Hagley and South 1983; Morse et al. 1981), but there is no information with which to determine whether the long-term

consequences of such exposures differ for adolescents versus adults, nor is there any information on the effects of hydrogen sulfide exposures in children and very little information on infants. Several developmental toxicity studies indicated that the exposure of pregnant rats and their pups to hydrogen sulfide resulted in structural and biochemical changes in the brain (Hannah and Roth 1991; Hannah et al. 1989, 1991). Subsequent work showed that many of the biochemical changes were transient; however, no studies were found that evaluated the behavioral consequences of these changes. Thus, a variety of studies are needed in order to determine whether children and infants are at risk from neurological deficits following hydrogen sulfide exposures *in utero* or during childhood and adolescence; information from such studies would also be useful in order to determine whether children are more sensitive to hydrogen sulfide exposure.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

A limited number of ongoing studies, designed to investigate mechanisms of hydrogen sulfide production in the digestive tract and potential health concerns, were identified in the Federal Research in Progress database (FEDRIP 2004). These studies are summarized below.

Dr. L. Chu, from the University of Texas Health Science Center, has designed studies to elucidate enzymatic mechanisms involved in hydrogen sulfide production by the oral bacterium, *Treponema denticola*, and to characterize the effects the hydrogen sulfide-induced effects on host inflammatory/ immune functions.

Dr. M. Levitt, from the Department of Veterans Affairs Medical Center in Minneapolis, Minnesota, has designed experiments in rats to investigate toxicity following the intestinal infusion of sodium sulfide. Dr. Levitt has also designed experiments to investigate the metabolic fate of hydrogen sulfide and other sulfur-containing compounds in the rat.

Dr. Fiedler and associates are investigating the neurological toxicity of hydrogen sulfide following low-level exposure.

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

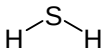
Information regarding the chemical identity of hydrogen sulfide is located in Table 4-1. This information includes synonyms, chemical formula and structure, and identification numbers.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of hydrogen sulfide is located in Table 4-2.

Hydrogen sulfide (H_2S) is a poisonous, colorless gas with a characteristic odor of rotten eggs. The odor threshold for hydrogen sulfide is variable and various ranges have been reported. Ruth (1986) reviewed odor thresholds of several hundred chemicals, including hydrogen sulfide, from the industrial hygiene literature and other compilations of odor threshold data; an odor threshold range of 0.0005–0.010 ppm was reported. Guidotti (1994) reported an odor threshold range of 0.01–0.3 ppm.

Table 4-1. Chemical Identity of Hydrogen Sulfide[a]

Characteristic	Information
Chemical name	Hydrogen sulfide
Synonyms/trade names	Hydrosulfuric acid; hydrogen sulphide, sewer gas, stink damp; sulfur hydride; sulfurated hydrogen; dihydrogen monosulfide; dihydrogen sulfide
Chemical formula	H2S
Chemical structure	
Identification numbers:	
CAS registry	7783-06-4
NIOSH/RTECS	MX1225000b
EPA hazardous waste	U135
DOT/UN/NA/IMCO shipping	UN1053; IMO 2.1
HSDB	576
EINECS	231-977-3
NCI	No data

[a]All information obtained from HSDB 2004 and ChemID 2004, except where noted.
[b]NIOSH 2004

CAS = Chemical Abstract Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EINECS = European Inventory of Existing Commercial Substances; EPA = Environmental Protection Agency; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Identity of Hydrogen Sulfide[a]

Property	Information
Molecular weight	34.08
Color	Colorless
Taste	Sweetish taste
Physical state	Gas
Melting point	-85.49 °C
Boiling point	-60.33 °C
Density in Air	1.19 (air=1.00)[b]
Density at 0 °C, 760 mmHg	1.5392 g/L
Odor	Rotten eggs
Odor threshold:	
Water	0.000029 ppm[c]
Air	0.0005–0.3 ppm[d,e]
Solubility:	
Water	5.3 g/L at 10 ºC; 4.1 g/L at 20 ºC; 3.2 g/L at 30 ºC[b]
Organic solvent(s)	Soluble in glycerol, gasoline, kerosene, carbon disulfide, crude oil
Partition coefficients:	
Log K_{ow}	Not applicable
Log K_{oc}	Not applicable
Vapor pressure at 25 °C	15,600 mm Hg[f]
Acid dissociation:	$H_2S(aq) \rightleftharpoons H^+(aq) + HS^-(aq)$ (1); $HS^-(aq) \rightleftharpoons H^+(aq) + S^{2-}(aq)$ (2)
pK_a (1)	7.04[b] $Ka_1 = \frac{[HS^-(aq)][H^+(aq)]}{[H_2S(aq)]}$
pK_a (2)	11.96[b] $Ka_2 = \frac{[S^{2-}(aq)][H^+(aq)]}{[HS^-(aq)]}$
Henry's law constant:	
at 20 °C	468 atm/mole fraction[g]
at 30 °C	600 atm/mole fraction[g]
at 40 °C	729 atm/mole fraction[g]
Autoignition temperature	500 °F (260 ºC)
Flammability limits	Upper, 44%; lower, 4.0% (by volume at room temperature)

Table 4-2. Physical and Chemical Identity of Hydrogen Sulfide[a]

Property	Information
Conversion factors	1 ppm = 1.40 mg/m^{3}[h]
Explosive limits	Upper, 45.5%; lower, 4.3% (by volume in air)

[a]All information obtained from HSDB 2004, except where noted.
[b]O'Neil et al. 2001
[c]Amoore and Hautala 1983
[d]Ruth 1986
[e]Guidotti 1994
[f]NIOSH 2004
[g]Daubert and Danner 1989
[h]Al-Haddad et al. 1989

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Natural gas and gases associated with crude oil contain varying amounts of hydrogen sulfide from trace amounts to 70–80%; gases containing hydrogen sulfide are referred to as sour gas (Pouliquen et al. 1989). Recovery of hydrogen sulfide from petroleum, natural gas, or manufactured gas operations is the main non-natural source of hydrogen sulfide. Recovery of hydrogen sulfide from petroleum, natural gas, and manufactured operations can be categorized into several methods. These include chemical and physical absorption, dry oxidation processes to form sulfur or oxides (Clause process), and liquid oxidation processes to form oxides (Ferrox process) (Beauchamp et al. 1984). Hydrogen sulfide can be produced by chemical reaction, reacting sulfur either with hydrogen gas (H_2) or with a hydrocarbon (Pouliquen et al. 1989). Another method of hydrogen sulfide recovery is hydrodesulfurization in which gas-oil and coke distillate fractions, which account for more than 90% of the sulfur in crude oil, are passed through a fixed-bed catalyst in the presence of hydrogen. Approximately 80–90% of the sulfur-containing compounds, mostly acyclic and cyclic sulfides, are converted into hydrogen sulfide by this process (Beauchamp et al. 1984; Weil and Sandler 1997). Hydrogen sulfide can also be produced by the hydrogen reduction or acid decomposition of a sulfide (Pouliquen et al. 1989). Current U.S. manufacturers of hydrogen sulfide are given in Table 5-1.

Hydrogen sulfide is not listed in the Toxics Release Inventory (TRI) as of August, 2004.

5.2 IMPORT/EXPORT

No data on import or export volumes for hydrogen sulfide are available.

5.3 USE

Hydrogen sulfide has a variety of industrial uses. Its major use is in the production of elemental sulfur and sulfuric acid. Sulfur recovered from the treatment of sour gas in 1986 accounted for 14 million tons, or 25% of the total world sulfur production. In 1995, the production of sulfuric acid was estimated to

Table 5-1. Current U.S. Manufacturers of Hydrogen Sulfide[a]

Company	Location
ATOFINA Chemicals, Inc.	
Thio and Fine Chemical Division	Houston, Texas
Montana Sulphur and Chemical Co.	Billings, Montana

[a]Derived from Stanford Research Institute (SRI) 2003, receipt where otherwise noted. SRI reports production of chemicals produced in commercial quantities (defined as exceeding 5,000 pounds or $10,000 in value annually) by the companies listed.

consume $1.1x10^5$ metric tons of hydrogen sulfide. More recent data on the consumption of hydrogen sulfide were not found. Hydrogen sulfide is used in the manufacture of metal sulfides and thioorganic compounds. Hydrogen sulfide is also used in the purification of nickel and manganese, in catalyst activation and poisoning, and in the treatment of metallic surfaces. It is used in metallurgy and in the production of heavy water for the nuclear industry. In the past, hydrogen sulfide was used as an agricultural disinfectant (Beauchamp et al. 1984; HSDB 2004; Weil and Sandler 1997).

5.4 DISPOSAL

Hydrogen sulfide is designated as a hazardous substance under Section 311(b) of the Clean Water Act (EPA 2004c). Disposal of wastes containing hydrogen sulfide is controlled by a number of federal regulations (see Chapter 8).

The EPA-assigned hazardous waste number for hydrogen sulfide is U135 (EPA 2004e). Generators of waste exceeding 100 pounds/month containing hydrogen sulfide must conform with the EPA regulations for the storage, transportation, treatment, and disposal of waste (EPA 2004c). Additional information concerning the accidental release of hydrogen sulfide and its reporting requirements is found in Chapter 8.

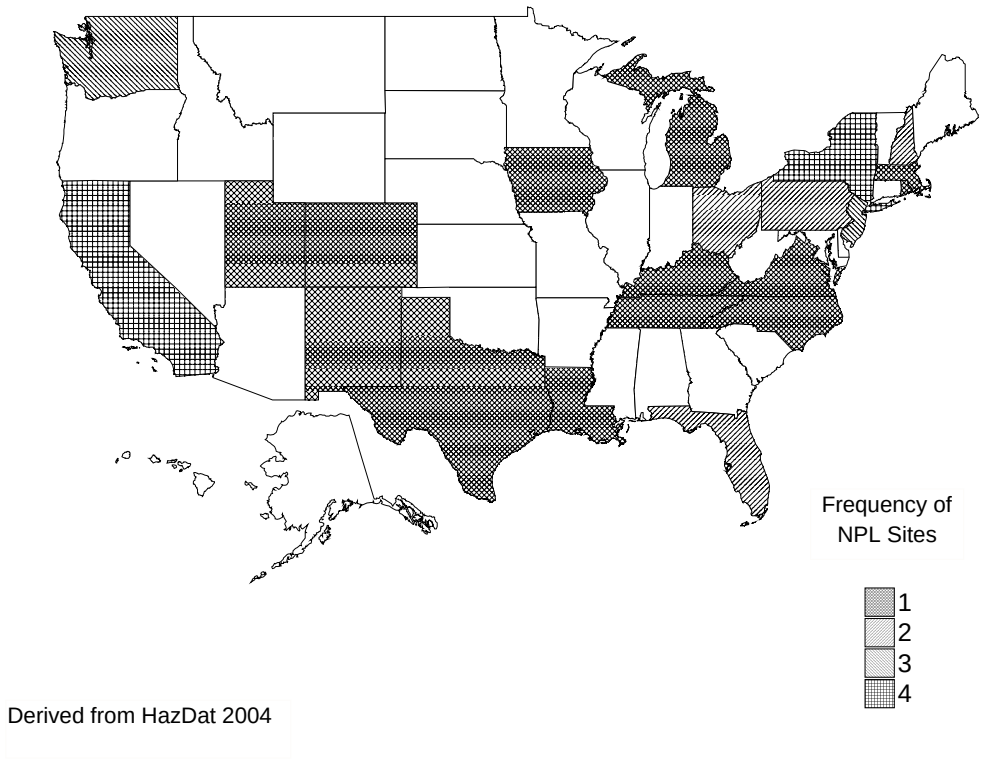
6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Hydrogen sulfide has been identified in at least 35 of the 1,647 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2004). However, the number of sites evaluated for hydrogen sulfide is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, all are located within the United States.

Hydrogen sulfide is one of the principal components in the natural sulfur cycle. Bacteria, fungi, and actinomycetes (a fungus-like bacteria) release hydrogen sulfide during the decomposition of sulfur containing proteins and by the direct reduction of sulfate (SO_4^{2-}). Hydrogen sulfide is also consumed by bacteria found in soil and water that oxidize hydrogen sulfide to elemental sulfur. Photosynthetic bacteria can oxidize hydrogen sulfide to sulfur and sulfate in the presence of light and the absence of oxygen (EPA 1993; WHO 1981). Hydrogen sulfide is commonly emitted from volcanoes, stagnant or polluted waters, and manure or coal pits with low oxygen content. These natural sources account for about 90% of the total hydrogen sulfide in the atmosphere (EPA 1993). Hydrogen sulfide may also enter the environment through accidental release, from leakage during manufacture or use, or as a result of industrial waste disposal. Because hydrogen sulfide is a natural component of petroleum, sulfur, and natural gas deposits, it may also be released into the environment during the extraction, transport, and refining of these resources. Landfills are another source of ambient hydrogen sulfide in the air (HazDat 2004; Lehman 1996). Sulfides, including hydrogen sulfide, constitute up to 1% by volume of typical landfill gases (Agency for Toxic Substances and Disease Registry 2001). The Fresh Kills Landfill on Staten Island, New York has been estimated to release approximately 16 tons of hydrogen sulfide to the air annually (Agency for Toxic Substances and Disease Registry 2000). Hydrogen sulfide is frequently found in industrial settings where it is either used as a reactant or is produced as a by-product of manufacturing or industrial processes. Examples of these processes are tanneries, waste water treatment facilities, manure and sewage facilities, rayon manufacturing plants, sulfur producers, coke oven plants, kraft paper mills, iron smelters, food processing plants, tar and asphalt manufacturing plants, and natural gas and petrochemicals plants (Fuller and Suruda 2000).

Figure 6-1. Frequency of NPL Sites with Hydrogen Sulfide Contamination



Degradation of hydrogen sulfide in the atmosphere can occur through oxidation by oxygen (O_2) and ozone (O_3) to give sulfur dioxide (SO_2), and ultimately, sulfate compounds. Sulfur dioxide and sulfates are eventually removed from the atmosphere through absorption by plants and soils or through precipitation (Hill 1973). Hydrogen sulfide in air can also react with photochemically generated hydroxyl radicals. The effective life-times for hydrogen sulfide based on summer daytime and yearly average hydroxyl radical concentrations have been estimated to be 0.23 and 2.3 days, respectively, based a measured rate constant of $4.8x10^{-12}$ cm^3/molecule second (Cox 1975). Life-times in air ranging from approximately 1 day in the summer to 42 days in the winter have been estimated for hydrogen sulfide (Bottenheim and Strausz 1980). Hydrogen sulfide is not expected to be decomposed by direct absorption of ultraviolet radiation, and the reaction with ozone is not expected to be a significant environmental fate (Cox 1975).

Hydrogen sulfide oxidation by O_2 may readily occur in surface waters (Millero et al. 1987, 1989). Hydrogen sulfide is readily soluble in water. In aqueous solution, hydrogen sulfide is a weak acid, exhibiting two acid dissociation constants. The first dissociation yields bisulfide ion (HS^-), and the second yields sulfide ion (S^{2-}), with pK_a values for each of these dissociations of 7.04 and 11.96, respectively (O'Neil et al. 2001). At a pH of 7.0, the ratio of the concentration of aqueous hydrogen sulfide to bisulfate ion is approximately 1-to-1. As the pH increases above 7.0, the ratio of the concentration of bisulfide ion to aqueous hydrogen sulfide increases. Only above pH 12 will the concentration of sulfide ion become significant (>50%). Hydrogen sulfide has been shown to sorb to various soils (Cihacek and Bremner 1993; Smith et al. 1973). Several species of soil, aquatic, and marine microorganisms oxidize hydrogen sulfide to elemental sulfur, and its half-time in these environments usually ranges from 1 hour to several hours (Jørgensen 1982). Because it is a gas under ambient conditions, bioconcentration and food chain biomagnification are unlikely (HSDB 2004).

Exposure of the general population to hydrogen sulfide most likely occurs through inhalation of ambient air. As hydrogen sulfide is part of the natural environment, the general population will have some exposure to hydrogen sulfide. Hydrogen sulfide is also produced in the human large intestine and by the natural bacteria found in the human mouth (Richardson et al. 2000; Rosenberg et al. 1991). Populations living in areas of geothermal activity, or near waste sites or industries such as petroleum refineries, natural gas plants, petrochemical plants, coke oven plants, kraft paper mills, food processing plants, landfills, manure treatment facilities, waste water treatment facilities, and tanneries are more likely to be exposed to higher levels of hydrogen sulfide. Facilities where hydrogen sulfide is produced, used, or generated include petroleum refineries, natural gas plants, petrochemical plants, coke oven plants, kraft

paper mills, viscose rayon manufacturing plants, sulfur production plants, iron smelters, food processing plants, manure treatment facilities, landfills, textile plants, waste water treatment facilities, and tanneries (Chénard et al. 2003; Devai and DeLaune 1999; Lehman 1996; Rimatori et al. 1996; Svendsen 2001); workers in these industries may be occupationally exposed to hydrogen sulfide.

6.2 RELEASES TO THE ENVIRONMENT

Hydrogen sulfide is not listed in the Toxics Release Inventory (TRI) as of August, 2004.

Hydrogen sulfide has been identified in a variety of environmental media (air, surface water, groundwater, soil, and sediment) collected at 35 of the 1,647 NPL hazardous waste sites (HazDat 2004).

6.2.1 Air

Hydrogen sulfide was identified in air collected at 23 of the 35 current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2004).

Hydrogen sulfide is produced naturally and as a result of human activity. Natural sources, such as swamps, bogs, and volcanoes, account for about 90% of the total amount of hydrogen sulfide in the atmosphere (EPA 1993). Annually, 100–324 million tons of hydrogen sulfide are released from natural sources with half from volcanoes, flooded ground, or hydrogeologically sources, and the other half from the oceans (Pouliquen et al. 1989). Many petroleum deposits and natural gas wells also contain hydrogen sulfide ("sour-gas wells") and become sources of atmospheric hydrogen sulfide release when developed (Layton and Cederwall 1986; Leahey and Schroeder 1986). Hydrogen sulfide is emitted by some plant species as a byproduct of sulfite metabolism (Takemoto et al. 1986; Wilson et al. 1978). Emission rates of various biogenic sulfur gases, including hydrogen sulfide, from the exposed soils of five wetland plant communities in Florida were measured during April, May, and October 1985 and January 1986. Emission rates for hydrogen sulfide varied from 0.1–1.0 to 8.3–152 µg sulfur/m^2/hour from a spike grass site in the Everglades National Park in January 1986 and a sawgrass site at Merritt Island National Wildlife Refuge in April 1985, respectively (Cooper et al. 1987). Hydrogen sulfide was identified in the volatile emissions of leaf litter of poplar trees (*Populus balsamifera*) (Isidorov and Jdanova 2002). Estimates of the terrestrial emission rate of hydrogen sulfide range from 58 to 110 million tons of

sulfur/year and estimates of the emission rate from oceans range from 30 to 170 million tons of sulfur/year (Hill 1973).

Hydrogen sulfide is chemically synthesized for use in the manufacture of rayon textiles, as an agricultural disinfectant, and as an additive in lubricants and cutting oils (HSDB 2004; Tyagi et al. 1988). It is a byproduct of kraft pulp and paper manufacturing and is used as an intermediate in the manufacture of sulfuric acid and inorganic sulfides (HSDB 2004; Kauppinen et al. 1997; Tyagi et al. 1988). Accidental release or improper disposal of materials resulting from these processes may result in hydrogen sulfide emissions. Ambient hydrogen sulfide concentrations in the air near landfills indicate that they are a source as well (HazDat 2004). Sulfides, including hydrogen sulfide, constitute up to 1% by volume of typical landfill gases (Agency for Toxic Substances and Disease Registry 2001). The Fresh Kills Landfill on Staten Island, New York has been estimated to release approximately 16 tons of hydrogen sulfide to the air annually (Agency for Toxic Substances and Disease Registry 2000). Facilities that treat manure may also release to hydrogen sulfide to the air. Hydrogen sulfide emissions were measured from two anaerobic lagoons used for treating swine waste; the overall mean hydrogen sulfide release was 5.7 $\mu g/m^2$/second (Lim et al. 2003).

6.2.2 Water

Hydrogen sulfide has been identified in groundwater and surface water at 3 and 1 site, respectively, of the 35 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2004).

Releases of hydrogen sulfide to water occur both naturally and as a result of human activity. Hydrogen sulfide released from aquatic plants, or as a result of anaerobic chemical processes in swamps and bogs, may dissolve in the water column or bind to clay or organic matter.

Hydrogen sulfide is chemically synthesized for use in the manufacture of rayon textiles, as an agricultural disinfectant, and as an additive in lubricants and cutting oils (HSDB 2004; Tyagi et al. 1988). It is a byproduct of kraft pulp and paper manufacturing and is used as an intermediate in the manufacture of sulfuric acid and inorganic sulfides (HSDB 2004; Tyagi et al. 1988). Discharge liquids from these and other activities can release hydrogen sulfide to receiving waters (EPA 1993).

6.2.3 Soil

Hydrogen sulfide has been identified in soil at 13 sites and in sediment at 3 sites among the 35 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2004).

Hydrogen sulfide may enter the soil through deposition from the atmosphere, migration of mobilized pore water, or from leaks and spills associated with manufacture, transport, or storage. Hydrogen sulfide is readily soluble in water and would exist as bisulfide or sulfide ions. Hydrogen sulfide can also form insoluble sulfide salts with various metals (i.e., copper, zinc, nickel, and iron) that may be present in soils (Pouliquen et al. 1989).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Since hydrogen sulfide exists as a gas at atmospheric pressure, partitioning to the air is likely to occur after environmental releases. However, the compound is also soluble in oil and water, and therefore, may partition as well to surface water, groundwater, or moist soil. In addition, sorption of hydrogen sulfide from air onto soil (Cihacek and Bremner 1993) and plant foliage (De Kok et al. 1983, 1988, 1991) occurs. Hydrogen sulfide's solubility in pure water varies with temperature from 5.3 g/L at 10 ºC to 3.2 g/L at 30 ºC. (O'Neil et al. 2001). Once hydrogen sulfide is dissolved in water, it will dissociate into bisulfide ion (HS^-) and sulfide ion (S^{2-}); the ratio of the concentrations of these various ions will depend on the pH of the solution. Hydrogen sulfide can also form insoluble sulfide salts with various metals (i.e., copper, zinc, nickel, and iron) that may be present in soils or environmental waters (Pouliquen et al. 1989).

Hydrogen sulfide evaporates easily from water, and the rate of evaporation depends on factors such as temperature, humidity, pKa, pH, and the concentration of certain metal ions. Hydrogen sulfide will cross the air-water interface with kinetics similar to other unreactive gases, such as oxygen (O_2), nitrogen (N_2), and carbon dioxide (CO_2), at pHs $\leq$6. At higher pHs, such as seawater, which has a pH of 8 or greater, hydrogen sulfide escape is enhanced due to an ionic species gradient in the water close to the surface (Balls and Liss 1983). The Henry's law constant was determined under a variety of conditions for hydrogen sulfide dissolved in sewage or distilled water and was found to increase linearly with temperature, indicating an increasing tendency to partition to the gas phase (Al-Haddad et al. 1989; also see Table 4-2). Other factors found to affect the Henry's law constant in sewage were pH, pK, flow rate,

and initial hydrogen sulfide concentration. Complexation of bisulfide and sulfide ions to trace metal ions (i.e., Zn^{2+}, Co^{2+}, and Ni^{2+}) found in seawater will also have an effect on the transport of hydrogen sulfide across the air-water interface (Elliot and Rowland 1990).

Clay or organic matter may sorb hydrogen sulfide. Smith et al. (1973) determined the sorption of hydrogen sulfide to six air-dried and moist soils in a laboratory study. The capacities of soil samples to sorb hydrogen sulfide ranged from 15.4 to 65.2 mg/g soil for the air-dried soils, and from 11.0 to 62.5 mg/g soil for the moist soils (50% water-holding capacity). Capacities and rates of sorption were not significantly affected by sterilization of the soil sample, indicating that soil microorganisms are not likely to be involved in the sorption process. The authors noted that these values, however, would not provide reliable estimates of the amounts of hydrogen sulfide that could be sorbed by soils under natural conditions, where the environmental fate of the sorbed hydrogen sulfide would have to be considered. Under natural conditions, it is likely that some of the hydrogen sulfide would be oxidized to sulfate, which may be removed by leaching or taken up by plants. This, in turn, may make gas sorption sites available for additional sorption (Smith et al. 1973). Cihacek and Bremner (1993) showed that soils can sorb considerable amounts of hydrogen sulfide from the air, retaining it as elemental sulfur. Several species of soil, aquatic, and marine microorganisms oxidize hydrogen sulfide to elemental sulfur, and its half-time in these environments usually ranges from 1 hour to several hours (Jørgensen 1982). Food chain bioconcentration and biomagnification are unlikely (HSDB 2004).

6.3.2 Transformation and Degradation

6.3.2.1 Air

In the atmosphere, hydrogen sulfide may be oxidized by oxygen (O_2) and ozone (O_3) to give sulfur dioxide (SO_2), and ultimately sulfate compounds. Sulfur dioxide and sulfates are eventually removed from the atmosphere through absorption by plants, deposition on and sorption by soils, or through precipitation (Hill 1973). A residence time of approximately 1.7 days at an ozone concentration of 0.05 mg/m^3 has been calculated for hydrogen sulfide (WHO 1981). The effective life-times for hydrogen sulfide based on summer daytime and yearly average hydroxyl radical concentrations have been estimated to be 0.23 and 2.3 days, respectively, based a measured rate constant of 4.8×10^{-12} cm^3/molecule second (Cox 1975). Life-times in air ranging from approximately 1 day in the summer to 42 days in the winter have been estimated for hydrogen sulfide (Bottenheim and Strausz 1980). Hydrogen sulfide is not

expected to be decomposed by direct absorption of ultraviolet radiation and the reaction with ozone is not expected to be a significant environmental fate (Cox 1975).

6.3.2.2 Water

In aqueous solution, hydrogen sulfide is a weak acid, exhibiting two acid dissociation constants. The first dissociation yields bisulfide ion (HS^-), and the second yields sulfide ion (S^{2-}), with pK_a values for each of these dissociations of 7.04 and 11.96, respectively (O'Neil et al. 2001). At a pH of 7.0, the ratio of the concentration of aqueous hydrogen sulfide to bisulfate ion is approximately 1-to-1. As the pH increases above 7.0, the ratio of the concentration of bisulfide ion to aqueous hydrogen sulfide increases. At a pH of 8, the ratio of the concentration of bisulfide ion to the concentration of aqueous hydrogen sulfide is approximately 10-to-1. Sulfide ion does not begin to appear until a pH of 11 is exceeded; only above pH 12 will the concentration of sulfide ion become significant (>50%).

Hydrogen sulfide oxidation by O_2 readily occurs in surface waters. At 25 ºC and pH 8, half-times of 50 and 26 hours were reported for hydrogen sulfide in water and seawater, respectively. Above pH 8, however, the rate of oxidation was independent of pH (Millero et al. 1987). Using a hydrogen peroxide concentration of $1x10^{-7}$ M as found in surface seawater, the half-time for sulfide oxidation by peroxide in seawater would be 2,800 hours. Only at hydrogen peroxide concentrations $>10^{-5}$ M, such as found in rainwaters, would the oxidation of hydrogen sulfide by hydrogen peroxide become competitive with the oxidation by oxygen (Millero et al. 1989). Hydrogen sulfide in waste water may be controlled by addition of oxidizing chemicals, which react to form harmless byproducts (Tomar and Abdullah 1994). In warm, damp environments (such as manholes and gravity sewers), hydrogen sulfide may be oxidized by autotrophic bacteria to sulfuric acid (Boon 1992). Chemical oxidation of hydrogen sulfide dissolved in sewage water produces sulfur at pH 6–7, while sulfur, polysulfides, thiosulfates, and ultimately sulfate are formed at pHs of 7–9 (Boon 1992).

6.3.2.3 Sediment and Soil

Hydrogen sulfide is one of the principal components in the natural sulfur cycle. Bacteria, fungi, and actinomycetes (a fungus-like bacteria) release hydrogen sulfide during the decomposition of sulfur containing proteins and by the direct reduction of sulfate (SO_4^{2-}). Hydrogen sulfide is also consumed by bacteria found in soil and water that oxidize hydrogen sulfide to elemental sulfur. Photosynthetic bacteria

can oxidize hydrogen sulfide to sulfur and sulfate in the presence of light and the absence of oxygen (EPA 1993; WHO 1981). A number of microorganisms have been found to degrade hydrogen sulfide to elemental sulfur or sulfate. Among these are a heterotrophic bacterium of the genus *Xanthomonas* isolated from dimethyl disulfide-acclimated peat (Cho et al. 1992), heterotrophic fungi (Phae and Shoda 1991), and a marine isopod (Vismann 1991). Soils may sorb considerable amounts of hydrogen sulfide from the air, retaining most of it in the form of elemental sulfur. Manganese compound found in these soils appeared to catalyze the oxidation of hydrogen sulfide to elemental sulfur (Cihacek and Bremner 1993).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to hydrogen sulfide depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. In reviewing data on hydrogen sulfide levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

6.4.1 Air

The concentration of hydrogen sulfide in air can be represented using various concentration units. All air monitoring data reported herein are reported in or have been converted into ppm or ppb for ease of comparison. The conversion factors are: 1 ppm=1.40 mg/m^3 and 1 ppb=1.40 $\mu g/m^3$.

Hydrogen sulfide ambient air concentrations from natural sources have been estimated to be between 0.11 and 0.33 ppb (EPA 1993). In an unpolluted area of Colorado, concentrations between 0.02 and 0.07 ppb were measured (Hill 1973). Near ground level, samples taken around a sulfurous New Zealand lake charged by an active underground geothermal vent had average hydrogen sulfide levels in the range of 0.125–3.9 ppm, which produced no visible adverse effects on indigenous bird or plant populations (Siegel et al. 1986). Hydrogen sulfide concentrations in air in remote marine environments are reported to be highly variable, ranging from 0.001 to 0.1 ppb (Elliot and Rowland 1990). Concentrations of hydrogen sulfide in urban areas are generally <1 ppb (Svendsen 2001). Hydrogen sulfide concentrations >90 ppb were measured during several intermittent periods in the Conimicut Point neighborhood in Warwick, Rhode Island that resulted from rotting seaweed and shellfish, after a "die-off" of aquatic plants

and animals that occurred in August 2003 in parts of the eastern Narragansett Bay. The concentration of hydrogen sulfide in the residential areas varied over time, depending on the tides, winds, and weather (Fulton et al. 2003).

Indoor air was monitored in five residential homes in the Dakota City/South Sioux City area in Nebraska from April 2 to May 15 1997. Hydrogen sulfide was routinely found in the indoor air of these homes. In general, hydrogen sulfide was found to not exceed 90 ppb, which was the upper detection limit for the measuring device used in this monitoring study; however, at one home, hydrogen sulfide was found to exceed the upper detection limit for periods of 20 minutes to more than 3 hours on 10 of the 30 days of sampling (Agency for Toxic Substances and Disease Registry 1997).

In early 1999, ATSDR and EPA conducted a 12-month hydrogen sulfide monitoring program in Dakota City. Sixteen hydrogen sulfide monitors were stationed in selected locations around the Dakota City area. White et al. (1999) noted that the frequency and concentration of hydrogen sulfide levels in Dakota City were higher than in a typical urban setting. During 6 months in 1999, peak hydrogen sulfide concentrations >90 ppb (the upper detection limit) were recorded at four monitoring locations, and three of these locations had multiple peak concentrations exceeding 90 ppb. Multiple peak levels in the range of 30–50 ppb were recorded for other residential areas. For three monitoring locations that were distant from a known source of hydrogen sulfide, peak levels of 9 and 19 ppb were recorded while most measurements were below the detection limit of 2 ppb (White et al. 1999).

An air monitoring study at a waste water treatment plant in Australia found time-averaged hydrogen sulfide levels of 1–2 ppm near the primary clarifiers and inlet structure, and levels <1 ppm at various other locations in the 10-hectare plant site (Koe 1985). Hydrogen sulfide was not detected by air-sampling instruments located around the perimeter of a landfill in Ohio after a major landslide occurred in March 1996 (Ingram et al. 1997). In a study to determine the quantity and composition of reduced sulfur gases, including hydrogen sulfide, being released to the atmosphere at waste water treatment plants in Baton Rouge, Louisiana at various steps of the treatment process, hydrogen sulfide was found to be the dominant sulfur compound emitted. The concentrations of hydrogen sulfide were typically <7.5 ppm sulfur, with concentrations ranging from 0.013 ppm sulfur at the central treatment plant final effluent box up to 340 ppm sulfur at the central treatment plant digester dome of the floating roof (Devai and DeLaune 1999). The hydrogen sulfide concentration in the atmosphere of a Norwegian sewage purification plant was generally below 2 ppm; however, a peak concentration of 100 ppm was detected (Søstrand et al. 2000). As part of the 1997 Fresh Kills Air Monitoring Program, more than 140,000 observations of

ambient air were collected over a 2-month period at 16 locations on Staten Island, New York. Hydrogen sulfide was measured at detectable levels in only about half of the samples, with measured levels ranging from 2 ppb (the detection limit) to 33 ppb (Agency for Toxic Substances and Disease Registry 2000).

Hydrogen sulfide concentrations in air can vary widely during manure management activities. Levels of hydrogen sulfide in air in pig barns during normal operations are generally <5 ppm; however, concentrations can rapidly rise up to 800 ppm inside manure transfer pits or lift stations when the manure is agitated, and the hydrogen sulfide can back up into pig rooms through open pits or piping. Concentrations of hydrogen sulfide have been shown to increase from very low levels to 1,300 ppm in deep-pit buildings when manure is agitated (Chénard et al. 2003).

The concentrations of sulfur compounds, including hydrogen sulfide, were measured in the air at four paper pulp mills using the kraft (sulfate) process. In this process, steam, high temperature, high pressure, and a solution containing sodium hydroxide and sodium sulfide is used to digest wood chips. Various sulfur gases are produced during this process. Hydrogen sulfide concentrations ranged from not detected (<0.2 ppm) to 35 ppm at various emission sources in the continuous digester, batch digester, and pulp washing areas. In general, hydrogen sulfide was not detected in ambient air sampled at these plants (Goyer 1990). A survey of occupational exposure in nonproduction departments of pulp, paper, and paper product mills from 147 mills in 11 countries found that hydrogen sulfide was below the detection limit in 45% of the 20 measurements taken at 6 mills. A mean concentration of 2.9 ppm was reported, with a maximum value of 53 ppm and a lowest detected value of 0.04 ppm (Teschke et al. 1999). The concentrations of various pollutants were measured in the air of five textile factories, which included three weaving and dyeing factories and two clothing factories; hydrogen sulfide concentrations ranged from <0.007 to 1.32 ppm (Rimatori et al. 1996).

Ten air samples were collected for hydrogen sulfide at the World Trade Center disaster site in New York City between September 18 and October 4, 2001. Concentrations ranged from not detected (3 of the 10 samples) to 3.0 ppm (Wallingford and Snyder 2001).

Hydrogen sulfide levels in air on some NPL sites ranged from 0.003 to 808 ppm at the Ellenville Scrap Iron and Metal facility in New York in 1998 and at the Seattle Municipal Landfill in Washington in 1985, respectively (HazDat 2004). Data on ambient air concentrations at all NPL sites were not available, however. Concentrations of hydrogen sulfide in soil gas from samples taken at some NPL sites ranged from 0.29 to 47,000 ppm, reported at Holly Hill Resource Facility in Connecticut in 1999 and at the

Industri-plex site in Massachusetts in 1990, respectively (HazDat 2004). Data on soil gas concentrations at all NPL sites were not available. It should be noted that concentrations in soil gas are likely to be higher than would be found in the breathing zone of an individual.

6.4.2 Water

Hydrogen sulfide readily evaporates from surface waters and is not likely to persist in highly oxygenated waters; levels in these environments are expected to be low. Groundwater samples from an area receiving acid-mine drainage in Colorado averaged 0.9 ppm of hydrogen sulfide, while samples from a power plant site averaged 0.03 ppm (Patterson and Runnells 1992).

Accurate measurements of hydrogen sulfide water levels are usually complicated by the presence of other sulfide compounds. At pHs ≥7, hydrogen sulfide is significantly dissociated, and the exact source of sulfide would not necessarily be known. A method of determining sulfide concentration in unspecified waste water by first transforming it to hydrogen sulfide and then measuring the atomic absorption of the product yielded results ranging from 3.1 to 5.1 ppm of sulfide sulfur (Parvinen and Lajunen 1994). Total sulfide levels in samples from the Mississippi River were about 0.92 ppm, while levels in pond and well water in St. Paul, Minnesota were 1.6 and 1.9 ppm, respectively (Slooff et al. 1991).

6.4.3 Sediment and Soil

Hydrogen sulfide levels as high as 11.7 ppm in soil water were measured in Louisiana rice fields (Hollis 1985). The hydrogen sulfide in these samples was presumably bound to colloidal clay or organic matter, as these levels were higher than typical solubility would predict and were not accompanied by the characteristic hydrogen sulfide odor. Sediment pore water from the Grand Calumet River in an industrialized area of Indiana contained 0.2–1.5 ppb of hydrogen sulfide (Hoke et al. 1993). In general, undisturbed anoxic sediment pore water may contain up to 100 ppb hydrogen sulfide, while disturbed sediments typically contain pore water concentrations of 1–30 ppb (Dillon et al. 1993).

6.4.4 Other Environmental Media

Hydrogen sulfide is commonly found in coal and petroleum deposits and may be mobilized by human manipulation of these resources. Coal gasification, a process whereby coal is subjected to heat and steam

treatment to produce a convenient energy source, results in a gas product consisting of up to 1% hydrogen sulfide (Barik et al. 1987). Hydrogen sulfide was identified as a component in the vapor phase of cigarette smoke (Dong et al. 2000), and was found in the emissions of gasoline vehicles (Collier et al. 2002).

Hydrogen sulfide formation has been demonstrated in pediatric intravenous amino acid solutions used to treat infants with high protein requirements (Decsi and Koletzko 1993). Levels up to 1.96 ppm were found, presumably formed by sulfide liberation from cysteine derivatives during heat sterilization. Similar chemical reactions may explain the presence of hydrogen sulfide in dental plaque (Tonzetich and Carpenter 1971). Meat products may be contaminated with hydrogen sulfide-producing bacteria, resulting in off-odors and spoilage (McMeekin and Patterson 1975).

Hydrogen sulfide is produced in the large intestine of mammals by metabolism of sulfhydryl proteins by anaerobic bacteria, and may compose up to 10% of intestinal gases (Beauchamp et al. 1984; EPA 1978). Hydrogen sulfide was found in the gas produced by feces of infants, and levels were found to vary based on the types of diets the infants were fed and the age of the infants. Fecal gas production for infants aged 1–3 months was 372–833, 73–371, and 1,904–2,540 nmol/g (12.7–28.3, 2.5–12.6, and 65.8–86.4 µg/g) dry weight for infants fed breast milk, milk-based formula, and soy based formula, respectively (Jiang et al. 2001). Fecal sulfide concentrations in 15 adult volunteers ranged from 110 to 720 nmol/g (3.74–24.5 µg/g) wet weight. Fecal sulfide concentrations were found to increase significantly from 160 to 750 nmol/g (5.4–26 µg/g), when subjects were fed diets containing increasing amounts of meat. Sulfide concentrations in whole blood samples from 6 healthy adults were found to range from 10 to 100 µmol/L (0.3–3 µg/mL). When increasing amounts of protein from meat were added to the diet of these subjects, blood sulfide concentrations did not change significantly (Richardson et al. 2000). Hydrogen sulfide is also produced in the human mouth by microbial putrefaction (Rosenberg et al. 1991). Mean sulfide levels in human brainstems controls were reported as 0.69 and 0.59 µg/g for males (n=36) and females (n=9), respectively. Sulfide concentrations of 0.91 and 1.04 µg/g were reported in brainstems from 2 suspected hydrogen sulfide inhalation fatalities (Goodwin et al. 1989). Concentrations of sulfide in the blood, brain, lung, and femoral muscle of a victim of a fatal hydrogen sulfide poisoning were 0.45 µg/mL, 2.72 µg/g, 0.42 µg/g, and 0.16 µg/g, respectively. The victim was kept at 0 ºC until autopsy, 20 hours after death; these conditions were expected to significantly suppress sulfide production due to putrefaction (Kage et al. 1998).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Primary exposure of the general population to hydrogen sulfide most likely occurs through inhalation of ambient air. As hydrogen sulfide is part of the natural environment, the general population will have some exposure to hydrogen sulfide. Hydrogen sulfide is produced in the human large intestine by the bacterial reduction of inorganic sulfate and sulfite, and by fermentation of sulfur-containing amino acids, cysteine, and methionine (Richardson et al. 2000), and can compose up to 10% of intestinal gases (EPA 1978). Hydrogen sulfide is produced by the natural bacteria found in the human mouth, and is a component of bad breath (halitosis) (Rosenberg et al. 1991).

Hydrogen sulfide may occur naturally in well water, and can be formed in hot water heaters, giving household hot tap water an unpleasant odor. Formation of hydrogen sulfide can occur by the reduction of sulfates in the water by sulfur bacteria, which thrive can in the warm environment of the hot water heater, or by reaction with the magnesium anode in the hot water heater tank (MDH 2004). Populations living in areas of geothermal activity, near waste sites or industries such as petroleum refineries, natural gas plants, petrochemical plants, coke oven plants, kraft paper mills, food processing plants, landfills, manure treatment facilities, waste water treatment facilities, and tanneries may be more likely to be exposed to higher levels hydrogen sulfide. The general population may also be exposed to hydrogen sulfide by accidental release ("blowout") from natural gas wells during drilling operations near residential areas (Layton and Cederwall 1986; Leahey and Schroeder 1986). Exposures to hydrogen sulfide have occurred through the mixing of acid and basic drain cleaners, and through the use of acid drain cleaner to remove sludge-clogged drains, but these incidents are thought to be rare (Oderda 1975).

Residents of the Conimicut Point neighborhood in Warwick, Rhode Island were exposed to hydrogen sulfide from rotting seaweed and shellfish, after a "die-off" of aquatic plants and animals that occurred on August 20, 2003 in parts of the eastern Narragansett Bay. The concentration of hydrogen sulfide in the residential areas varied over time, depending on the tides, winds, and weather. During the week of September 15, 2003, the Rhode Island Department of Environmental Management measured several intermittent periods when hydrogen sulfide concentrations were >90 ppb (Fulton et al. 2003). Emissions from the Fresh Kills Landfill on Staten Island, New York, which contain hydrogen sulfide, are blown by prevailing wind into nearby neighborhoods (Agency for Toxic Substances and Disease Registry 2000).

Workers may be occupationally exposed to hydrogen sulfide from fermenting manure (Chénard et al. 2003; Morse et al. 1981), and stagnant wells (McDonald and McIntosh 1951), as well as in areas of

waste-water treatment facilities (NIOSH 1980b, 1984, 1985a, 1985d, 1990), extruded rubber plants (NIOSH 1985b), landfills (Lehman 1996), textile industries (Rimatori et al. 1996), and petroleum refineries (NIOSH 1982a, 1982b). Facilities where hydrogen sulfide can be generated include petroleum refineries, natural gas plants, petrochemical plants, coke oven plants, kraft paper mills, viscose rayon manufacturing plants, sulfur production facilities, iron smelters, food processing plants, and tanneries (Svendsen 2001). Hydrogen sulfide was found to be responsible for 16 of 87 toxic inhalation fatalities of construction workers between 1990 and 1999 (Dorevitch et al. 2002).

Toxic exposure data for 1995, compiled from 67 poison control centers, indicated that there were 1,407 hydrogen sulfide exposures during that year, 3 of which were intentional exposures (Litovitz et al. 1996). None of these individuals died, and the vast majority of these exposures resulted in outcomes that were either minor or nonexistent. Approximately 34% of the exposed individuals were treated in a health care facility (Litovitz et al. 1996).

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Hydrogen sulfide is found naturally in crude petroleum, natural gas, volcanic gases, hot springs, and often as the result of bacterial breakdown of organic matter. Children are more likely to be exposed to hydrogen sulfide near animal waste sites such as the sediments of fish aquaculture, livestock barns, or manure areas. Inhalation is the most likely route of exposure, and there are no known exposure pathways that are unique to children, although hydrogen sulfide is heavier than air so that children might be exposed to higher concentrations than adults. Children living in areas of geothermal activity, near waste

sites or industries such as petroleum refineries, natural gas plants, petrochemical plants, coke oven plants, kraft paper mills, food processing plants, and tanneries are more likely to be exposed to higher levels of hydrogen sulfide. In a clinical case involving a 20-month-old child whose parents lived beside a coal mine where a burning tip had been emitting hydrogen sulfide for nearly 1 year, the patient had symptoms of ataxia and an abnormal CT scan of the brain (Gaitonde et al. 1987). Monitoring data showed that the hydrogen sulfide levels in the air were approximately 0.6 ppm, but may have been higher before data were collected.

Hydrogen sulfide is also produced by bacteria in the mouth and gastrointestinal tract. Hydrogen sulfide formation has been demonstrated in pediatric intravenous amino acid solutions used to treat infants with high protein requirements (Decsi and Koletzko 1993). Levels up to 1.96 ppm were found, presumably formed by sulfide liberation from cysteine derivatives during heat sterilization.

There are no known studies in which hydrogen sulfide levels were measured in the blood or other tissues of children. Hydrogen sulfide was found in the gas produced by feces of infants, and levels were found to vary based on the types of diets the infants were fed and the age of the infants. Fecal gas production for infants aged 1–3 months were 372–833, 73–371, and 1,904–2,540 nmol/g (12.7–28.3, 2.5–12.6, and 65.8–86.4 µg/g) dry weight for infants fed breast milk, milk based formula, and soy based formula, respectively (Jiang et al. 2001).

It is not clear whether hydrogen sulfide can be transferred from mother to fetus. There is limited evidence that women occupationally exposed to hydrogen sulfide have a higher rate of spontaneous abortions. Women employed in rayon textile and paper products jobs in Finland were found to have an increased rate of spontaneous abortions when the mean annual level of hydrogen sulfide exceeded 3 ppb (Hemminki and Niemi 1982). An increase in spontaneous abortions was also found in women working in petrochemical plants in China as compared to women working in non-chemical plants (Xu et al. 1998).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers employed at facilities that manufacture or use hydrogen sulfide in the production process are especially prone to exposure. Such industries include the manufacture of rayon textiles, lubricants, pulp and paper, and sulfuric acid and inorganic sulfides. Workers in facilities where hydrogen sulfide is produced as a byproduct, such as farms with manure storage pits, petroleum or natural gas drilling operations, landfills, and waste water treatment plants, may also be exposed to high levels.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of hydrogen sulfide is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of hydrogen sulfide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. Information is available on the physical and chemical properties of hydrogen sulfide (Al-Haddad et al. 1989; Amoore and Hautala 1983; Daubert and Danner 1989; HSDB 2004; NIOSH 2004; O'Neil et al. 2001). However, additional information on those properties that determine the specific fate, transport, and rates of transformation of hydrogen sulfide as part of the larger sulfur cycle would be useful in discerning the environmental fate and behavior of this compound.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The TRI, which contains this information for 2002, became available in 2004. This database will be updated yearly and should provide a list of industrial production facilities and emissions. However, hydrogen sulfide is not required to be reported under the TRI.

Adequate information on the production and use of hydrogen sulfide was found; no information on the import/export of hydrogen sulfide was located.

Environmental Fate. Hydrogen sulfide is known to easily evaporate into the air (EPA 1993; Layton and Cederwall 1986; Leahey and Schroeder 1986), although its solubility in water may also cause it to persist in unperturbed, anoxic sediments. Additional information on the transport, transformation, and persistence of the compound in soils and groundwater, particularly at hazardous waste sites, would be useful in identifying the most important routes of human exposure to hydrogen sulfide.

Bioavailability from Environmental Media. Additional information on absorption following dermal contact with, or ingestion of, contaminated soil and water would also be helpful in determining the importance of this route of exposure for populations of concern.

Food Chain Bioaccumulation. Sufficient information is available to demonstrate that hydrogen sulfide is not likely to bioaccumulate or biomagnify in the food chain.

Exposure Levels in Environmental Media. Monitoring of hydrogen sulfide levels in ambient air is currently sporadic; additional, more systematic sampling is needed, particularly in areas that may have a significant source of hydrogen sulfide. Methods for accurately measuring dissolved sulfides in water are also available (APHA 1998). As hydrogen sulfide is a weak acid, concentrations of aqueous hydrogen sulfide will depend on the pH of the solution. The concentration of un-ionized hydrogen sulfide can be calculated from the concentration of dissolved sulfide components, the pH of the solution, and the acidity constants for hydrogen sulfide (APHA 1998). Reliable monitoring data for the levels of hydrogen sulfide in contaminated media at hazardous waste sites are needed so that the information obtained on levels of hydrogen sulfide in the environment can be used in combination with the known body burdens of hydrogen sulfide to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. More data on the levels of hydrogen sulfide at the point of emission (on-site) versus levels at the point of exposure (off-site) would be useful.

Exposure Levels in Humans. Occupational studies often do not report exposure levels. Additional information is needed on the exposure levels among populations living in the vicinity of hazardous waste sites and other potential sources of hydrogen sulfide, such as hot springs and waste water treatment plants.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. The only information that provided an assessment of exposure of children and adolescents to hydrogen sulfide was that developed during the South Karelia Air Pollution Study in southeastern Finland where there are a cluster of pulp mills using the sulfate method (Marttila et al. 1994b); however, determining the magnitude of these exposures was complicated by the study's analysis of only gross sulfur concentrations rather than measuring the concentrations of individual sulfur-containing compounds and particulates. Additional exposure information is needed from communities where only hydrogen sulfide exceeds background levels.

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for hydrogen sulfide were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

No ongoing studies pertaining to the environmental fate of hydrogen sulfide were identified in a search of the Federal Research in Progress database (FEDRIP 2004).

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring hydrogen sulfide, its metabolites, and other biomarkers of exposure and effect to hydrogen sulfide. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

A limited number of analytical techniques have been used for measuring hydrogen sulfide in the breath (expired air) and sulfide in biological tissues and fluids including blood and saliva. These include gas chromatography coupled with flame ionization detection (GC/FID), gas chromatography coupled with flame photometric detection (GC/FPD), iodometric titration, potentiometry with ion-selective electrodes (ISE), spectrophotometry, and high-performance liquid chromatography (HPLC). The measurement of sulfide concentrations in biological materials is difficult due to its volatility, tendency to undergo oxidation, adsorption to glass and rubber, and binding to organic molecules (Richardson et al. 2000). Details of commonly used analytical methods for several types of biological media are presented in Table 7-1.

In air, hydrogen sulfide will exist in its molecular form, and methods are available to measure hydrogen sulfide in air. However, in aqueous solution, hydrogen sulfide is a weak acid, exhibiting two acid dissociation constants. The first dissociation yields bisulfide ion (HS^-), and the second yields sulfide ion (S^{2-}), with pK_a values for each of these dissociations of 7.04 and 11.96, respectively (O'Neil et al. 2001). In biological tissues and fluids, sulfide concentrations typically would be determined. The concentration of the un-ionized hydrogen sulfide can be calculated from the concentration of dissolved sulfide components, pH of the solution, and acidity constants for hydrogen sulfide using the equilibrium expressions for the ionization of hydrogen sulfide and bisulfide ion (APHA 1998).

Table 7-1. Analytical Methods for Determining Hydrogen Sulfide, Sulfide, and Thiosulfate in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit[a]	Percent recovery	Reference
Blood	Hydrogen sulfide in generated in Kipp's apparatus and trapped in NaOH solution; pH is adjusted to 6.5–6.8, azide and excess iodine are added.	Iodometric method	4 µg/L	98–102	Puacz et al. 1995
Blood	Hydrogen sulfide in generated in Kipp's apparatus and trapped in NaOH solution; sulfide antioxidation buffer is added.	Potentiometry (ISE)	NR	98–102	Puacz et al. 1995
Blood	Liberation of blood sulfide by addition of acid; trapping of hydrogen sulfide gas in NaOH solution.	ISE	10 µg/L	NR	Lindell et al. 1988
Blood and urine	For thiosulfate detection, add 0.2 mL sample to mixture of 0.5 mL of 20 mM pentafluoro-benzyl bromide (PFBBr) solution in acetone, 0.05 mL of 5% sodium chloride. Vortex for 1 minute and add 2 mL of 25 mM iodine solution in ethyl acetate and 0.5 mL of internal standard solution (40 µM 1,3,5-tribromobenzene [TBB] in ethyl acetate). Vortex 30 seconds and centrifuge at 2,500 rpm for 15 minutes, allow to stand for 1 hour.	GC/ECD	3 µmol/L	NR	Kage et al. 1997
Blood and urine	For sulfide detection, add 0.2 mL sample to mixture of 0.5 mL of 20 mM PFBBr solution in toluene, 2.0 mL of internal standard solution (10 µM TBB in ethyl acetate), and 0.8 mL of 5 mM tetradecyl-dimethylnenzyl ammonium chloride solution in oxygen-free water saturated with sodium tetraborate. Vortex 1 minute, add 0.1 g potassium dihydrogenphosphate as a buffer. Vortex for 10 seconds, centrifuge at 2,500 rpm for 10 minutes.	GC/ECD	0.3 µmol/L	NR	Kage et al. 1997

Table 7-1. Analytical Methods for Determining Hydrogen Sulfide, Sulfide, and Thiosulfate in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit[a]	Percent recovery	Reference
Urine	Freeze and store freshly voided urine samples at -25 °C until analysis within 24 hours after exposure. Analyze urinary thiosulfate as its bromobimane product. Correct results for the excreted creatinine analyzed in the same samples.	LC	NR	92, 80	Kangas and Savolainen 1987
Blood and feces	Addition of zinc acetate to trap sulfide, followed by microdistillation into NaOH solution to trap evolved hydrogen sulfide; analysis by ion chromatography.	IC/ECD	2.5 µmol/L	92–102 (feces) 79–102 (blood)	Richardson et al. 2000
Breath	Connect Teflon sampling probe to analyzer and syringe through a sampling valve and loop; insert probe 4 cm into mouth between closed lips; withdraw 20 mL over 6 seconds into syringe; flush and fill the sample loop with 10 mL mouth air; carry sample to analysis in nitrogen gas.	GC/FID	10 µg/m^3 (7 ppb)	NR	Blanchette and Cooper 1976
Breath	Collect air from breathing zone using a midget impinger containing calcium hydroxide-calcium sulfide-arabinogalactan slurry; add solution of N,N-dimethyl-p-phenylenediamine and ferric chloride.	Spectro-photometry	0.20 µg/m^3 (0.1 ppb)	80	NIOSH 1977a
Saliva	Collect 3 mL aliquot with sterile pipette; introduce into 2-ounce glass container and cap; incubate 24 hours at 37 °C; withdraw through cap with gas-tight syringe.	GC/FID, microcoulo-metric titration	NR	NR	Solis and Volpe 1973

Table 7-1. Analytical Methods for Determining Hydrogen Sulfide, Sulfide, and Thiosulfate in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit[a]	Percent recovery	Reference
Brain, lung, and femoral muscle	For sulfide detection, add 0.2 g sample (minced) to mixture of 0.5 mL of 20 mM PFBBr solution in toluene, 2.0 mL of internal standard solution (10 µM TBB in ethyl acetate), and 0.8 mL of 5 mM tetradecyl-dimethylnenzyl ammonium chloride solution in oxygen-free water saturated with sodium tetraborate. Vortex 1 minute, add 0.1 g potassium dihydrogenphosphate as a buffer. Vortex for 10 seconds, centrifuge at 2,500 rpm for 10 minutes.	GC/MS	NR	NR	Kage et al. 1998
Brain, lung, and femoral muscle	For thiosulfate detection, add 0.2 g sample (minced) to mixture of 0.5 mL of 20 mM PFBBr solution in acetone, 0.05 mL of 5% sodium chloride and 0.5 mL of 200 mM L-ascorbic acid. Vortex for 1 minute and add 2 mL of 25 mM iodine solution in ethyl acetate and 0.5 mL of internal standard solution (40 µM TBB in ethyl acetate). Vortex 30 seconds and centrifuge at 2,500 rpm for 15 minutes, allow to stand for 1 hour.	GC/MS	NR	NR	Kage et al. 1998
Brain, liver, and kidney tissue (mouse)	Weight sample; homogenize in aqueous zinc acetate using a rotostator at 18,000 rpm for 20 seconds; dilute with borate buffer; convert to methylene blue.	Ion-interaction reversed-phase HPLC	nmol/g	NR	Mitchell et al. 1993

Table 7-1. Analytical Methods for Determining Hydrogen Sulfide, Sulfide, and Thiosulfate in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit[a]	Percent recovery	Reference
Brain tissue (rat and human)	Homogenization in coid 0.01 M NaOH. Centrifuge and resuspend pellet; add zinc acetate and ascorbic acid; readjust pH; use continuous flow gas dialysis system to separate sulfide.	Gas dialysis/ion chromato-graphy with ECD	0.02 µg/g	95–99 (rat tissue)	Goodwin et al. 1989

[a]Conversion factor: 1 ppm=1.40 mg/m^3

GC/ECD = gas chromatography/electron capture detector; GC/FID = gas chromatography/flame ionization detector; GC/MS = gas chromatography/mass spectrometry; HPLC = high performance liquid chromatography; IC = ion chromatography; ISE = ion-selective electrode; LC = liquid chromatography; M = molar; NaOH = sodium hydroxide; NR = not reported; PFBBr = pentafluorobenzyl bromide; rpm = revolutions per minute; TBB = 1,3,5-tribromobenzene

$$Ka_1 = \frac{[HS^-(aq)][H^+(aq)]}{[H_2S(aq)]}$$

$$Ka_2 = \frac{[S^{2-}(aq)][H^+(aq)]}{[HS^-(aq)]}$$

Puacz et al. (1995) developed a catalytic method, based on the iodine-azide reaction, for the determination of sulfide in whole human blood. The method involves the generation of hydrogen sulfide in an evolution-absorption apparatus. In addition, the method allows for the determination of sulfide in blood without interference from other sulfur compounds in blood. This method is appropriate for the determination of sulfide in the concentration range of 4–3,000 µg/L. A percent recovery of 98–102% was achieved. Although the accuracy and precision of the catalytic method are comparable to those of the ion-selective electrode method, the catalytic method is simpler, faster, and would be advantageous in serial analysis.

Richardson et al. (2000) developed a method for measuring sulfide in whole blood and feces, which overcomes the problems of viscosity and turbidity that are typical for these types of samples. Turbidity of the sample interferes with colorimetric assays such as methylene blue. In this new method, samples are first treated with zinc acetate to trap the sulfide as an insoluble zinc complex. Next, a microdistillation pretreatment is used to release the complexed sulfide into a sodium hydroxide solution. This microdistillation step is coupled to ion chromatography with electron capture detection. A detection limit of 2.5 µmol/L (80 µg/L) and percent recoveries of 92–102% (feces) and 79–102% (blood) were reported.

GC/FPD was employed for measuring hydrogen sulfide in human mouth air with a detection sensitivity capable of 7 ppb (Blanchette and Cooper 1976) and included improvements such as calibration of the system with permeation tubes, use of a variable beam splitter to produce a wide range of vapor concentrations, and the ability to handle samples of limited volume.

For occupational measurements of airborne concentrations, NIOSH (1977a) recommended the use of a midget impinger for sampling breathing zone air and the methylene blue/spectrophotometric method for the analysis of hydrogen sulfide. The detection limit was 0.14 ppb.

GC/FID has been used for quantifying sulfur volatiles such as hydrogen sulfide in human saliva (Solis and Volpe 1973). This method included microcoulometric titrations and a procedure for incubation of saliva and sampling of headspace sulfur volatile components. The amount of total sulfur volatiles detected in control samples of saliva incubated at 37 °C for 24 hours ranged from 4.55 to 13.13 ppm.

Fresh and frozen mouse tissue samples obtained from brain, liver, and kidney have been analyzed for hydrogen sulfide levels by sulfide-derived methylene blue determination using ion-interaction reversed-phase HPLC (Mitchell et al. 1993). This method can quantify nmol/g levels of sulfide. Gas dialysis/ion chromatography with ECD has been utilized for measurement of sulfide in rat brain tissue with 95–99% recovery (Goodwin et al. 1989). Goodwin et al. (1989) also applied this method to human brain tissue samples from two suspected hydrogen sulfide fatalities.

7.2 ENVIRONMENTAL SAMPLES

The methods most commonly used to detect hydrogen sulfide in environmental samples include GC/FPD, gas chromatography with electron capture detection (GC/ECD), iodometric methods, the methylene blue colorimetric or spectrophotometric method, the spot method using paper or tiles impregnated with lead acetate or mercuric chloride, ion chromatography with conductivity, and potentiometric titration with a sulfide ion-selective electrode. Details of commonly used analytical methods for several types of environmental samples are presented in Table 7-2.

Several methods for determining hydrogen sulfide in air have been investigated. GC/FPD has been widely used for analyses of hydrogen sulfide at levels ranging from 10^{-11} to 10^{-8} grams/0.56 mL (EPA 1978; Stetter et al. 1977). Sampling of a standard reference (0.055 ppm hydrogen sulfide) with this method resulted in a relative standard deviation of <3% (WHO 1981). The sensitivity of hydrogen sulfide detection in air was improved with GC/ECD (Stetter et al. 1977). The detector operation is based upon the measurement of the current when hydrogen sulfide is electrochemically oxidized at a diffusion electrode. Use of this method resulted in a lower detection limit of $3x10^{-12}$ grams hydrogen sulfide and a precision of 0.5%. Analyses were achieved within 2 minutes. GC/FPD has been used to measure hydrogen sulfide that has been removed from air by activated carbon fiber (Choi et al. 1991). Activated carbon fiber, made from coal tar, effectively oxidized hydrogen sulfide (200 ppm) to sulfate.

Methylene blue techniques have been widely utilized for continuous, quantitative monitoring of hydrogen sulfide in air and are sensitive to hydrogen sulfide concentrations down to approximately 1–3 ppb

Table 7-2. Analytical Methods for Determining Hydrogen Sulfide and Sulfide in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit[a]	Percent recovery	Reference
Air	Filter through a 0.5 µm Zefluor; absorb on a solid sorbent tube containing shell charcoal; desorb with ammonia hydroxide and hydrogen peroxide; dilute.	Ion chromatography, conductivity	11 µg/sample; working range 0.6–14 ppm for a 20-L air sample	NR	NIOSH 1994b (Method 6013)
Air	Aspirate through cadmium hydroxide; precipitate as cadmium sulfide; add STRactan 10®; react with N,N-dimethyl-p-phenylene-diamine and ferric chloride to yield methylene blue.	Spectrophotometry	0.20 µg/m^3	80	Adams et al. 1975; EPA 1978; NIOSH 1977a
Air	Aspirate through sodium hydroxide and ethanol; react with N,N-dimethyl-p-phenylenediamine and ferric chloride to yield methylene blue.	Spectrophotometry	No data	NR	Van den Berge et al. 1985
Air	Absorb onto cadmium(II)-exchange zeolite; precipitate as cadmium sulfide; convert to methylene blue; measure at 750 nm.	PAS	0.01 µg	NR	NIOSH 1979
Air	Electrochemically oxidize sample at potential-controlled Teflon-bonded diffusion electrode.	GC/ECD	3 pg	NR	Stetter et al. 1977
Air	Introduce sampled air and carrier gas onto column.	GC/FPD	5–13 µg/m^3	NR	EPA 1978
Air	Introduce sample onto column packed with activated carbon filter.	GC/FPD	No data	NR	Choi et al. 1991
Air	Absorb in an impinger containing a standardized solution of iodine and potassium iodide; titrate with standard sodium thiosulfate solution.	Iodometric titration	No data	NR	EPA 1978
Air	Trap H_2S in an aqueous NaOH and ascorbic acid in a midget impinger; titrate resulting sulfide ion with $CdSO_4$ solution.	Potentiometry	ppb levels	NR	Ehman 1976

Table 7-2. Analytical Methods for Determining Hydrogen Sulfide and Sulfide in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit[a]	Percent recovery	Reference
Air	Aspirate through ammoniacal cadmium chloride; strip sulfur dioxide by aeration; dissolve cadmium sulfide; precipitate in concentrated HCl; titrate with iodine using a starch indicator.	Iodometric titration	0.7 µg/L	NR	EPA 1978
Air	Filter measured volume of air through lead-acetate-impregnated filter paper tape; compare optical density with unexposed impregnated spot of similar area.	Lead-acetate-impregnated filter paper tape	No data	NR	EPA 1978
Air	Filter measured volume of air through mercuric chloride-impregnated filter paper tape; compare optical density with unexposed impregnated spot of similar area.	Mercuric chloride-impregnated filter paper tape	0.7 µg/m^3 (0.5 ppb)	NR	EPA 1978
Air	Pass air through silver membrane filter.	Silver membrane filters/optical density measurements	No data	NR	EPA 1978
Water	Add an amine-sulfuric acid reagent and a ferric chloride solution to the sample, mix gently; after 3–5 minutes add $(NH_4)_2HPO_4$ solution; analyze after 3–15 minutes.	Colorimetry	Applicable to sulfide concentrations ranging from 0.1 to 20.0 mg/L	89–92	APHA 1998 (Methylene Blue Method)
Water	For unpreserved samples, add solutions of zinc acetate, sodium hydroxide, and ascorbic acid, shake and let stand for 30 minutes; for preserved samples, omit the zinc acetate step.	Spectro-photometry	Applicable at sulfide concentrations from 0.002 to 0.100 mg/L	97.6–104.2	APHA 1998 (Gas Dialysis, Automated Methylene Blue Method)
Water	To the sample, add an excess of standard iodine solution; back titrate with a sodium thiosulfate solution.	Iodometric titration	Accurate method for determining sulfide concentrations >1 mg/L	NR	APHA 1998 (Iodometric Method)

Table 7-2. Analytical Methods for Determining Hydrogen Sulfide and Sulfide in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit[a]	Percent recovery	Reference
Water	Add an alkaline antioxidant reagent (AAR) and zinc acetate to the sample; measure the potential and compare to a calibration curve.	ISE	Applicable for sulfide concentrations >0.03 mg/L	NR	APHA 1998 (ISE Method)
Water	Collect water sample; acidify; strip sample with helium; collect gas in nitrogen-cooled trap.	GC/FPD	0.6 pmol/L	NR	Radford-Knoery and Cutter 1993
Water and sludge	Acidify sample to convert sulfide ion to hydrogen sulfide; measure hydrogen sulfide absorption at 196.0 nm using the selenium atomic line.	AAS	0.25 µg (1–10 mL sample volume)	NR	Parvinen and Lajunen 1994
Sediment	Acidify sample to convert sulfide ion to hydrogen sulfide; trap hydrogen sulfide in sodium hydroxide; sulfide reacts with N,N-dimethyl-p-phenylene-diamine to form methylene blue.	Colorimetry	0.01 µmol/g	NR	Allen et al. 1994
Sediment	Trap in silver nitrate solution as insoluble silver sulfide.	Gravimetry	10 µmol/g	NR	Allen et al. 1994
Sediment	Trap in a sulfide antioxidant buffer.	Potentiometry/ ISE	No data	NR	Allen et al. 1994

[a]Conversion factor: 1 ppm=1.40 mg/m^3

AAR = alkaline antioxidant reagent; AAS = atomic absorption spectroscopy; $CdSO_4$ = cadmium sulfate; GC/ECD = gas chromatography/electron capture detector; GC/FPD = gas chromatography with flame photometric detection; HCl = hydrochloric acid; H_2S = hydrogen sulfide; ISE = ion-selective electrode; NaOH = sodium hydroxide; NR = not reported; PAS = photoacoustic spectroscopy

(NIOSH 1977a). This method provides adequate specificity with good accuracy and precision (WHO 1981). The amount of sulfide is determined by spectrophotometric or colorimetric measurement of methylene blue. The method has been improved to eliminate the formation of the precipitate cadmium sulfide, which can result in the obstruction of the sampling impinger (Van Den Berge et al. 1985). Also, the simplified method can be used to measure hydrogen sulfide levels in the viscose rayon industry because it is not as sensitive to carbon disulfide. Limitations of the methylene blue method include potential interferences from light, mercaptans, sulfides, nitrogen dioxide, and sulfur dioxide, and that the system is not portable (NIOSH 1977a). Photoacoustic spectroscopy of hydrogen sulfide converted to methylene blue has been demonstrated to yield greater sensitivity than standard spectrophotometric methods (NIOSH 1979). By maximizing instrument response to the 750-nm peak, it was possible to achieve a detection limit of 0.01 µg when collected at 2.0 L/minute for a 1-hour period.

NIOSH (method 6013) describes the measurement of hydrogen sulfide in the air by ion chromatography (NIOSH 1994b). This method has a working range of 0.6–14 ppm for a 20-L air sample and an estimated limit of detection of 11 µg per sample. However, sulfur dioxide may interfere with the measurement of hydrogen sulfide.

The iodometric method has also been utilized in analyzing hydrogen sulfide in the air (EPA 1978). The method is based on the oxidation of hydrogen sulfide by absorption of the gas sample in an impinger containing a standardized solution of iodine and potassium iodide. This solution will also oxidize sulfur dioxide. The iodometric method is suitable for occupational settings. The accuracy of the method is approximately 0.50 ppm hydrogen sulfide for a 30-L air sample (EPA 1978).

Paper tapes impregnated with lead acetate have been widely used for air sample measurements of hydrogen sulfide in the field (EPA 1978; WHO 1981). The presence of other substances capable of oxidizing lead sulfide can lead to errors. This method has been improved by impregnating the paper with mercuric chloride or silver nitrate (EPA 1978; WHO 1981). Mercuric chloride paper tape is sensitive and reliable for measurement of hydrogen sulfide in air with a sensitivity of 0.7 µg/L (EPA 1978). Tapes impregnated with silver nitrate are suitable for determination of hydrogen sulfide concentrations in the range of 0.001–50 ppm (WHO 1981).

Potentiometric titration with a sulfide ion-selective electrode as an indicator has been used to measure hydrogen sulfide in the air at ppb levels (Ehman 1976). The method has been shown to have very good accuracy and precision. No interference could be found from nitrogen dioxide, sulfur dioxide, or ozone.

Passive card monitors can be used to detect hydrogen sulfide in workplace environments (Saunders et al. 2002). These monitors can be categorized as quantitative, semiquantitative, and indicator cards. Quantitative cards use an optical reader to assess exposure and calculate a hydrogen sulfide concentration in air; the results are digitally displayed. Semiquantitative cards are read by comparing the exposed card to a chart or by observing a progressive color development in windows on the card that represent differing exposure concentration ranges. The indicator cards change color above a certain threshold concentration of hydrogen sulfide. Saunders et al. (2002) reported detection limits of 4–8 and 0.8–4 ppm-hours for two commercial quantitative card monitors, 1 and 0.1 ppm-hours for two commercial semiquantitative card monitors, and 0.05 and 0.4 ppm-hour for two commercial indicator card monitors.

The APHA (1998) defines three categories of sulfides that must be taken into account for analytical methods measuring sulfides in water: total sulfide, dissolved sulfide, and un-ionized hydrogen sulfide. Total sulfide includes all sulfide containing species, dissolved hydrogen sulfide, bisulfide ion, and acid-soluble metal sulfides in suspended matter. Dissolved sulfide includes sulfide-containing components that remain after suspended solids have been removed. The concentration of the un-ionized hydrogen sulfide can be calculated from the concentration of dissolved sulfide components, pH of the solution, and the acidity constants for hydrogen sulfide using the equilibrium expressions for the ionization of hydrogen sulfide and bisulfide ion (APHA 1998).

Samples that contain sulfide species can be either analyzed immediately after collection, or preserved with a zinc acetate solution for later analysis (APHA 1998). The addition of zinc ion (Zn^{2+}) to the sample will precipitate any sulfides as zinc sulfide. A qualitative sulfide test, such as a precipitation test using potassium antimony tartrate or testing for hydrogen sulfide vapors using lead acetate paper or silver foil, can be useful and are advisable when testing industrial wastes that may contain substances that interfere with certain test methods, such as the methylene blue method (APHA 1998).

The total sulfide concentration in a water sample can be determined using an iodometric titration. In this method sulfide is reacted with a measured excess of iodine in an acidic solution; the remaining unreacted iodine is then determined by titration with a thiosulfate solution. This method is an accurate method for determining sulfide concentrations of >1 mg/L, if interferences are absent and the loss of hydrogen sulfide from the solution is avoided. The iodometric method is best suited for the analysis of samples freshly taken (i.e., from wells and springs) (APHA 1998).

The methylene blue method is applicable to sulfide concentrations ranging from 0.1 to 20.0 mg/L. In this method, an amine-sulfuric acid reagent and a ferric chloride solution are added to the sample to produce methylene blue, which is then quantified colorimetrically. In the automated methylene blue method, a gas dialysis technique separates the sulfide from the sample matrix, which removes most inferences (i.e., turbidity and color). Addition of ascorbic acid, an antioxidant, improves sulfide recovery. The automated methylene blue method is applicable at sulfide concentrations from 0.002 to 0.100 mg/L (APHA 1998).

Potentiometric methods using a silver electrode are also suitable for determination of sulfide concentrations in water and are unaffected by sample color or turbidly. In this method, an alkaline antioxidant reagent (AAR) and zinc acetate are added to the sample. The potential of the sample is measured using an ion selective electrode (ISE) and the measurement is compared to a calibration curve. This method is applicable for sulfide concentrations >0.03 mg/L (APHA 1998).

Three methods for quantifying acid volatile sulfides in sediment have been described (Allen et al. 1994). These include methylene blue/colorimetric methods, gravimetry, and potentiometry with ion-selective electrode. Prior to measurement, the acid volatile sulfide in the sample is converted to hydrogen sulfide by acidification. The hydrogen sulfide is then purged from the sample and trapped in aqueous solution for the colorimetric and potentiometric methods. In the gravimetric method, hydrogen sulfide is trapped with silver nitrate ($AgNO_3$), and the mass of the insoluble silver sulfide (Ag_2S) that is formed is determined. The methylene blue/colorimetric method is generally preferred and is capable of determining acid volatile sulfide concentrations in sediment as low as 0.01 µmol/g (0.3 µg/g) dry weight. The gravimetric method can be used for samples with moderate or high acid volatile sulfides. However, below concentrations of acid volatile sulfides in dry sediment of 10 µmol/g (320 µg/g), accuracy may be affected by incomplete recovery of precipitate or by weighing errors. The limit of detection of the ion-selective electrode method as applied to measuring hydrogen disulfide in sediment was not reported.

GC/FPD has been used to measure hydrogen sulfide, free (uncomplexed) sulfide, and dissolved metal sulfide complexes in water (Radford-Knoery and Cutter 1993). Hydrogen sulfide was measured in the headspace of the sample (100 mL) with a detection limit of 0.6 pmol/L (20 pg/L). A detection limit of 0.2 pmol/L (6 pg/L) was obtained for total dissolved sulfide. This method allows for the determination of the concentration of free sulfide that is in equilibrium with hydrogen sulfide. Complexed sulfide can be estimated from the difference between total dissolved sulfide and free sulfide.

A molecular absorption spectrophotometry method, using a sharp-line irradiation source, has been developed for the determination of sulfide (as hydrogen sulfide) in water and sludge samples. The method was tested with measurements of real waste water samples. The limit of detection was 0.25 µg (1–10 mL sample volume) (Parvinen and Lajunen 1993).

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of hydrogen sulfide is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of hydrogen sulfide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Methods are available for measuring hydrogen sulfide in expired air (Blanchette and Cooper 1976; NIOSH 1977a). Methods are available for measuring sulfide in blood (Puacz et al. 1995; Richardson et al. 2000) and brain tissue (Goodwin et al. 1989) and measuring sulfur volatiles in saliva (Solis and Volpe 1973). Methods are available for measuring thiosulfate levels in urine (Kage et al. 1992; Kangas and Savolainen 1987; Milby and Baselt 1999). Analytical methods with satisfactory sensitivity and precision are available to determine levels of hydrogen sulfide and thiosulfate in human tissues and body fluids. Methods that can quantitatively correlate levels in biological fluids and tissues with environmental exposure levels would be helpful in estimating exposure to hydrogen sulfide.

Effect. No methods have been identified that can be used to directly associate levels of hydrogen sulfide in biological samples with the onset of adverse health effects.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods are available for measuring hydrogen sulfide in air (Ehman 1976; EPA 1978; NIOSH 1977a, 1979, 1994b; Stetter et al. 1977; Van Den Berge et al. 1985; WHO 1981). Methods are available for measuring sulfide in sediment (Allen et al. 1994), water, (APHA 1998; Radford-Knoery and Cutter 1993), and sludge (Parvinen and Lajunen 1994). Since hydrogen sulfide is part of the natural environment, dissociates in aqueous solution, and can bind to various metal ions in environmental media, in most cases, it would not be possible to distinguish the specific source of sulfide ions in environmental media. In the event of a release of hydrogen sulfide, increased sulfide concentrations in surrounding environmental media would likely be due to the release.

7.3.2 Ongoing Studies

No ongoing studies pertaining to analytical methods for hydrogen sulfide were identified in a search of the Federal Research in Progress database (FEDRIP 2004).

8. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding hydrogen sulfide in air, water, and other media are summarized in Table 8–1.

An acute-duration inhalation MRL of 0.2 ppm was derived for hydrogen sulfide. This MRL is based on a minimal LOAEL of 2 ppm for a greater than 30% alteration in two measures of lung function that are suggestive of bronchial obstruction (airway resistance and specific airway conductance) in 2 out of 10 persons with asthma (Jappinen et al. 1990). Although two measures of lung function were altered in two of the subjects, there were no statistically significant alterations in lung function for the whole group. The MRL was derived by dividing the unadjusted LOAEL by an uncertainty factor of 9 (3 for the use of a minimal LOAEL and 3 for human variability). Further details on the derivation of this MRL can be found in the MRL worksheets in Appendix A of this profile.

An intermediate-duration inhalation MRL of 0.02 ppm was derived for hydrogen sulfide. This MRL is based on a NOAEL of 10 ppm and a LOAEL of 30 ppm for olfactory neuron loss and basal cell hyperplasia in the nasal olfactory epithelium of rats exposed for 6 hours/day, 7 days/week for 10 weeks (Brenneman et al. 2000). The NOAEL was adjusted for intermittent exposure and multiplied by the regional gas dose ratio (RDGR) for extrathoracic effects to calculate a human equivalent concentration (HEC). The MRL was derived by dividing the $NOAEL_{HEC}$ by an uncertainty factor of 30 (3 to extrapolate from animal to human using dosimetic adjustment and 10 to account for human variability). Further details on the derivation of this MRL can be found in the MRL worksheets in Appendix A of this profile.

EPA has derived a chronic inhalation reference concentration (RfC) for chronic exposure to hydrogen sulfide. The RfC of 0.002 mg/m^3 (0.001 ppm) is based on a NOAEL of 13.9 mg/m^3 (10 ppm) and a LOAEL of 41.7 mg/m^3 (30 ppm) for nasal lesions of the olfactory mucosa in rats (Brenneman et al. 2000). The $NOAEL_{HEC}$ of 0.64 mg/m^3 was divided by an uncertainty factor of 300 (3 for interspecies extrapolation with dosimetric adjustment from rat to human, 10 for sensitive populations, and 10 for subchronic exposure) (IRIS 2004).

Table 8-1. Regulations and Guidelines Applicable to Hydrogen Sulfide

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No data	
WHO	Air quality guideline (averaging time of 24 hours)	0.15 mg/m^3	WHO 2000
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	10 ppm	ACGIH 2003
	STEL	15 ppm	
EPA	Accidental release prevention; threshold quantity	10,000 pounds	EPA 2004a 40CFR68.130
NAC	Interim AEGL-1[a]		EPA 2004k
	10 minutes	0.75 ppm	
	30 minutes	0.60 ppm	
	60 minutes	0.51 ppm	
	4 hours	0.36 ppm	
	8 hours	0.33 ppm	
	Interim AEGL-2[b]		
	10 minutes	41 ppm	
	30 minutes	32 ppm	
	60 minutes	27 ppm	
	4 hours	20 ppm	
	8 hours	17 ppm	
	Interim AEGL-3[c]		
	10 minutes	76 ppm	
	30 minutes	59 ppm	
	60 minutes	50 ppm	
	4 hours	37 ppm	
	8 hours	31 ppm	
NIOSH	REL (10-minute ceiling TWA)	10 ppm	NIOSH 2004
	IDLH	100 ppm	
OSHA	Acceptable ceiling concentration	20 ppm	OSHA 2004e 29CFR1910.1000, Table Z-2
	Acceptable maximum peak above the acceptable ceiling concentration for an 8-hour shift		
	Concentration	50 ppm	
	Maximum duration	10 minutes once, only if no other measured exposure occurs	

Table 8-1. Regulations and Guidelines Applicable to Hydrogen Sulfide

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
OSHA	PEL (8-hour TWA) for construction industry	10 ppm	OSHA 2004c 29CFR1926.55, Appendix A
	PEL (8-hour TWA) for shipyard industry	10 ppm	OSHA 2004a 29CFR1915.1000, Table Z
	Highly hazardous chemicals that present a potential for a catastrophic event at or above the threshold quantity	1,500 pounds	OSHA 2004b 29CFR1910.119, Appendix A
b. Water			
	Designated as a hazardous substances pursuant to Section 311(b) of the Clean Water Act		EPA 2004j 40CFR116.4
	Reportable quantity of hazardous substance designated pursuant to Section 311(b) of the Clean Water Act	100 pounds	EPA 2004g 40CFR117.3
c. Food			
No data			
d. Other			
EPA	Carcinogenicity classification	No data	IRIS 2004
	RfC	$2x10^{-3}$ mg/m^3	
	RfD	Withdrawn	
	Superfund; extremely hazardous substances; threshold quantity	500 pounds	EPA 2004d 40CFR355, Appendix A
	Superfund; designated as a hazardous substance pursuant to Section 311(b)(2) of the Clean Water Act; reportable quantity	100 pounds	EPA 2004c 40CFR302.4
STATE			
a. Air			
Minnesota	Ambient air quality standard	0.05 ppm	Minnesota PCA
Wisconsin	Hazardous air contaminant; acceptable ambient concentration for emission rate		Wisconsin DNR 2004
	<25 feet	1.1664 pounds/hour	
	≥25 feet	4.8960 pounds/hour	
	Ambient air standard	335 µg/m^3	
b. Water			
Wisconsin	Drinking water guideline	30 µg/L	HSDB 2004

Table 8-1. Regulations and Guidelines Applicable to Hydrogen Sulfide

Agency	Description	Information	Reference
STATE *(cont.)*			
c. Food			
No data			
d. Other			
No data			

[a]AEGL-1 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.
[b]AEGL-2 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long lasting adverse health effects or an impaired ability to escape.
[c]AEGL-3 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening adverse health effects or death.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = Acute Exposure Guideline Level; CFR = Code of Federal Regulations; DNA = Department of Natural Resources; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NAC = National Advisory Committee; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PCA = Pollution Control Agency; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; RfC = reference concentration; RfD = reference dose; STEL = short-term exposure limit; TLV = threshold limit values; TWA = time-weighted average; USC = United States Codes; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD10 would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration(Lo) (LC_{Lo})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration(50) (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose(Lo) (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose(50) (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time(50) (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose(50) (TD50)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used;

however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Hydrogen Sulfide
CAS Number: 7783-06-4
Date: September 17, 2004
Profile Status: Final Pre-Public Comment Draft
Route: [x] Inhalation [ ] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 16
Species: Human

Minimal Risk Level: 0.2 [ ] mg/kg/day [x] ppm

Reference: Jäppinen P, Vikka V, Marttila O, et al. 1990. Exposure to hydrogen sulphide and respiratory function. Br J Intern Med 47:824-828.

Experimental design: This study evaluated lung function in three male and seven female subjects with bronchial asthma requiring medication for 1–13 years; none of the subjects had severe asthma. The subjects were exposed to 2 ppm hydrogen sulfide for 30 minutes. Respiratory function in response to a histamine challenge was assessed prior to exposure and after exposure.

Effects noted in study and corresponding doses: No statistically significant changes in forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and forced expiratory flow were noted. Airway resistance (Raw) and specific airway conductance (SGaw) did not show statistically significant changes when examined as a group. In two subjects, there were changes of over 30% in both Raw and SGaw; these changes were suggestive of bronchial obstruction. Additionally, 3 of 10 subjects complained of headaches after exposure.

Dose and end point used for MRL derivation:

[ ] NOAEL [X] LOAEL

At 2 ppm, no statistically significant alterations in lung function were observed. However, 2 of 10 individuals showed changes in airway resistance and specific airway conductance in excess of 30%.

Uncertainty Factors used in MRL derivation:

[x] 3 for use of a minimal LOAEL
[ ] 10 for extrapolation from animals to humans
[x] 3 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? None.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: None.

Other additional studies or pertinent information which lend support to this MRL: Bhambhani et al. (1996b) evaluated the acute effects of hydrogen sulfide on the physiological and hematological health of male and female volunteers exposed to 5 ppm during two 30-minute sessions of submaximal exercise (50% of maximum aerobic power). No significant changes in any parameter were noted in the women,

whereas the men showed a significant decrease in muscle citrate synthetase as well as nonsignificant changes in lactate, lactate dehydrogenase, and cytochome oxidase. Together, these changes were considered indicative of compromise of aerobic metabolism.

No respiratory or cardiovascular effects were observed in 16 male volunteers exposed by oral inhalation to hydrogen sulfide at 0.5, 2, or 5 ppm for more than 16 minutes while exercising (Bhambhani and Singh 1991). The end points examined included heart rate, oxygen uptake, carbon dioxide output, and blood gases. Airway resistance and conductance were not measured in this study. No significant changes in pulmonary function parameters were noted in individuals exposed to 10 ppm hydrogen sulfide for 15 minutes during exercise (Bhambhani et al. 1996).

Respiratory distress was noted in two workers exposed to >40 ppm hydrogen sulfide for under 25 minutes (Spolyar 1951). In animals, impacts on the respiratory system such as increases in the cellularity and lactate dehydrogenase and alkaline phosphatase activities of bronchial lavage fluids have been seen at exposures as low as 10 ppm for 4 hours (Lopez et al. 1987), although without a dose-related trend.

A significant dose-related decrease in lung microsomal cytochrome c oxidase activity was seen in rats following a 4-hour exposure to 50, 200, or 400 ppm hydrogen sulfide (Khan et al. 1990). Similarly, succinate oxidase activity also decreased in a dose-related fashion; although no affect was observed at the lowest dose. Cytochrome oxidase levels returned to normal by 24 hours postexposure in animals in the 200 ppm group, but not the 400 ppm group. Exposure at the two higher dose levels was also associated with complete abolition of the zymosan-induced stimulation of respiratory rates of pulmonary alveolar macrophages and there were significant decreases in the number of viable macrophages in lung lavage fluids at the highest dose (Khan et al. 1991). Rats exposed to much higher levels (375 or 399 ppm for 4 hours) developed moderate to massive pulmonary edema (Prior et al. 1990).

Agency Contact (Chemical Manager): Selene Chou

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Hydrogen Sulfide
CAS Number: 7783-06-4
Date: September 17, 2004
Profile Status: Final Pre-Public Comment Draft
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 39
Species: Sprague-Dawley rats

Minimal Risk Level: 0.02 [ ] mg/kg/day [x] ppm

Reference: Brenneman KA, James RA, Gross EA, et al. 2000. Olfactory neuron loss in adult male CD rats following subchronic inhalation exposure to hydrogen sulfide. Toxicol Pathol 28:326-333.

Experimental design: Groups of male Sprague-Dawley rats (12/group) were exposed to 0, 10, 30, or 80 ppm hydrogen sulfide 6 hours/day, 7 days/week for 10 weeks. End points examined were limited to the nose; six transverse levels of the nose were examined via light microscopy.

Effects noted in study and corresponding concentrations: Nasal lesions were limited to the olfactory mucosa in rats exposed to 30 or 80 ppm and consisted of multifocal, bilaterally symmetrical olfactory neuron loss and basal cell hyperplasia affecting the lining of the dorsal medial meatus and the dorsal and medial regions of the ethmoid recess. In most cases, the incidence, mean severity, and distribution of exposure-related lesions increased in a concentration-related manner. The severity of the olfactory lesions were scored as 1 mild, 2 moderate, or 3 severe. For the olfactory neuron loss, the mild, moderate, or severe severity scores corresponded to 26–50, 51–75, and 76–100%, respectively, reduction in the normal thickness of the olfactory neuron layer; for the basal cell hyperplasia, mild, moderate, or severe severity scores corresponded to 1–33, 34–67, or 68–100% of the normal thickness of the olfactory neuron cell layer replaced by basal cells. The basal cell hyperplasia is a regenerative response to the loss of olfactory neurons. No olfactory lesions were observed in the controls or rats exposed to 10 ppm. At 30 ppm, the olfactory neuron loss was observed at nasal levels 4 (11/12, severity 1.4) and 5 (9/12, severity 1.1) and basal cell hyperplasia was observed at nasal levels 4 (10/12, severity 1.8) and 5 (11/12, severity 1.3). At 80 ppm, olfactory neuron loss was observed at levels 3 (8/8, severity 2.4), 4 (12/12, severity 2.4), 5 (11/12, severity 1.5), and 6 (5/12, severity 1.2; incidence not statistically significant) and basal cell hyperplasia was observed at nasal levels 4 (12/12, severity 1.2), 5 (11/12, severity 1.3), and 6 (6/12, severity 1.0).

Dose and end point used for MRL derivation:

[x] NOAEL [ ] LOAEL

The MRL is based on a NOAEL of 10 ppm and a LOAEL of 30 ppm for olfactory neuron loss and basal cell hyperplasia in the olfactory epithelium of the nose.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[x] 3 for extrapolation from animals to humans with dosimetric adjustment
[x] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? None.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

$NOAEL_{ADJ}$ =10 ppm x 6 hour/24 hour x 7 days/7 days=2.5 ppm

The human equivalent concentration (HEC) was calculated using the following equation (EPA 1994b):

$$NOAEL_{HEC} = NOAEL_{ADJ} \times RDGR_{ET}$$

The regional gas dose ratio for the extrathoracic region ($RGDR_{ET}$) of 0.184 was calculated using the following equation:

$$RGDR_{ET} = \frac{\left(\frac{V_E}{SA_{ET}}\right)_{rat}}{\left(\frac{V_E}{SA_{ET}}\right)_{human}}$$

Where:
V_e is the minute volume and SA_{ET} is the surface area of the extrathoracic (ET) region of the respiratory tract.

Minute volume (V_e)

Human: 13.8 L/minute (EPA 1994b)
Rat: 0.190 L/minute; calculated using the following EPA equation:

$$\ln(V_e) = b_0 + b_1 \ln(BW)$$

For rats, b_0 equals -0.578 and b_1 equals 0.821
Because a limited amount of body weight data were reported in the study, a reference body weight of 0.267 kg (EPA 1988) was used.

EPA (1994b) rat and human respiratory surface area reference values:

Extrathoracic	15.0 cm^2 (rat)	200 cm^2 (human)

$$NOAEL_{[HEC]} = NOAEL\ (ADJ) \times RGDR = 2.5\ ppm \times 0.184 = 0.46\ ppm$$

Other additional studies or pertinent information which lend support to this MRL: There are limited data on the toxicity of hydrogen sulfide in humans following intermediate-duration exposure. Acute- and chronic-duration studies suggest that the respiratory tract, cardiovascular system, and nervous system are sensitive targets of hydrogen sulfide.

Intermediate-duration animal studies support the identification of the respiratory tract and nervous system as sensitive targets; cardiovascular effects have not been reported in intermediate-duration animal studies. Exposure of rats and mice to low hydrogen sulfide concentrations have resulted in histological damage to

the upper respiratory tract. Brenneman et al. (2000) reported significant concentration-related increases in the incidence and severity of lesions to the nasal olfactory epithelium in rats exposed to hydrogen sulfide for 10 weeks. The effects consisted of olfactory neuron loss and basal cell hyperplasia in rats exposed to 30 ppm and higher, 6 hours/day, 7 days/week for 10 weeks; no adverse effects were observed at 10 ppm. An earlier studies conducted by CIIT (1983b, 1983c) did not find significant alterations in the nasal turbinates of Sprague-Dawley or F-344 rats exposed to ≤80 ppm hydrogen sulfide 6 hours/day, 5 days/week for 13 weeks. Inflammation of the squamous portion of the nasal mucosa was observed in mice exposed to 80 ppm hydrogen sulfide 6 hours/day, 5 days/week for 13 weeks (CIIT 1983a); the NOAEL for this effect is 30 ppm. However, a re-examination of the histological specimens from this study (Dorman et al. 2004) revealed significant increases in the incidence of olfactory neuron loss in male and female Sprague-Dawley rats, F-344 rats, and B6C3F_1 mice exposed to 30 or 80 ppm; the NOAEL was 10 ppm. Additionally, significant increases in the incidence of bronchiolar epithelial hypertrophy and hyperplasia were observed in female Sprague-Dawley rats exposed to 30 or 80 ppm and male Sprague-Dawley rats and male F-344 rats exposed to 80 ppm. The sensitivity of the olfactory epithelium has been confirmed by acute-duration studies. Degeneration of the olfactory epithelium was observed in rats exposed to 400 ppm hydrogen sulfide for 4 hours (Lopez et al. 1988b), rats exposed to 200 ppm for 3 hours (Brenneman et al. 2002), and rats exposed to 80 ppm 3 hours/day for 5 days (Brenneman et al. 2002). Data collected using a computational fluid dynamics model of the rat nasal epithelium (Moulin et al. 2002) suggest that the olfactory epithelium is more sensitive than the nasal respiratory epithelium despite the higher hydrogen sulfide flux (a surrogate for dose) to the regions lined with respiratory epithelium compared to regions lined with olfactory epithelium. Within the areas of the nose lined with olfactory epithelium, a high correlation between predicted hydrogen sulfide flux and the incidence of olfactory lesion was found.

The neurotoxicity of hydrogen sulfide following intermediate-duration exposure has not been adequately tested in mature animals; the data are limited to studies assessing brain weight, neurological function (posture, gait, tone of facial muscles, and pupillary reflexes), and histopathology. A 5% decrease in absolute brain weight was observed in Sprague-Dawley rats exposed to 80 ppm hydrogen sulfide 6 hours/day, 5 days/week for 13 weeks; no alterations were observed at 30 ppm (CIIT 1983c). No alterations in histopathology or neurological function were observed in Sprague-Dawley rats (CIIT 1983c), F-344 rats (CIIT 1983b), or B6C3F_1 mice (CIIT 1983a) exposed to concentrations up to 80 ppm 6 hours/day, 5 days/week for 13 weeks. Neurodevelopmental toxicity studies have found some alterations that are suggestive of neurotoxicity. The suggestive findings in the offspring of rats exposed to 20 ppm 7 hours/day on gestational day 5 through postnatal day 21 include alterations in the architecture and growth characteristics of Purkinje cell dendritic fields (Hannah and Roth 1991), decreases in norepinephrine and increases in serotonin in the frontal cortex (Skrajny et al. 1992), and decreases in brain amino acid levels were observed at 75 ppm (Hannah et al. 1989, 1990). However, no alterations in neurobehavioral performance (assessed via motor activity, passive avoidance, acoustic startle, functional observation battery) were observed in the offspring of rats exposed for 2 weeks prior to mating, during mating, on gestational days 5–19, and on postnatal days 5–18 (Dorman et al. 2000). These data suggest that exposures of 20–80 ppm may result in subclinical alterations in neurochemistry.

Agency Contact (Chemical Manager): Selene Chou

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not

meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system,

which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

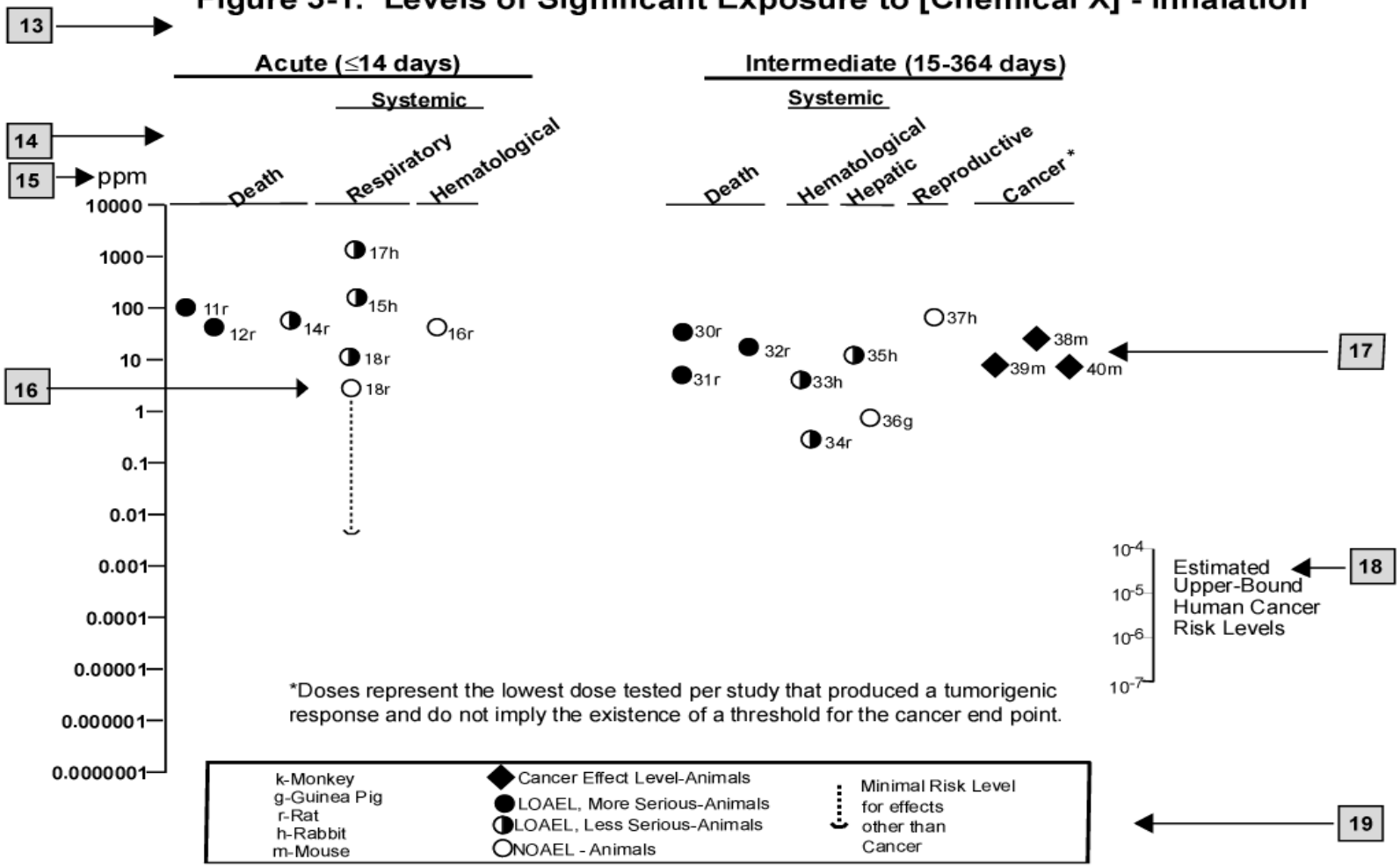
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FEV_1	forced expiratory volume in 1 second
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FVC	forced vital capacity
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans*,*trans*-muconic acid
MAL	maximum allowable level

mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA

OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SIR	standardized incidence ratio
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TRS	total reduced sulfur
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
VO_2	oxygen uptake

VCO_2	carbon dioxide uptake
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D. INDEX